

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-268**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA 22-268

SUPPL # N/A

HFD # 590

Trade Name Coartem®

Generic Name artemether/lumefantrine

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

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

YES  NO

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

505 (b)(1)

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

YES  NO

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

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

d) Did the applicant request exclusivity?

YES  NO

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

5

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

YES  NO

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

N/A

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

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

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2

YES

NO

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

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

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

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

Investigation #1

IND #

YES

!

!

! NO

! Explain:

Investigation #2

IND #

YES

!

!

! NO

! Explain:

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

interest provided substantial support for the study?

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

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

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

YES  NO

If yes, explain:

=====  
Name of person completing form: Gregory DiBernardo  
Title: Regulatory Project Manager  
Date: 3/30/09

Name of Office/Division Director signing form: Renata Albrecht, M.D.  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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Renata Albrecht  
3/30/2009 05:15:11 PM

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA: 22-268 Supplement Number: Not Applicable NDA Supplement Type (e.g. SE5): Not Applicable  
Division Name: Special Pathogen and Transplant Products PDUFA Goal Date: 12/27/08 Stamp Date: 6/27/08  
Proprietary Name: Coartem  
Established/Generic Name: (artemether/lumefantrine)  
Dosage Form: 20 mg/120 mg combination Tablet  
Applicant/Sponsor: Novartis Pharmaceuticals Corporation  
Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only): (1) Not Applicable  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Treatment of infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*

**Q1:** Is this application in response to a PREA PMC/PMR? Yes  Continue  
No  Please proceed to Question 2.  
If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMC/PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMC/PMR?  
 Yes. Please proceed to Section D.  
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

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

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?  
 Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A:</b> Fully Waived Studies (for all pediatric age groups)
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Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

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Gregory DiBernardo  
Regulatory Project Manager

(Revised: 6/2008)

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

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Gregory F DiBernardo  
12/12/2008 04:20:09 PM  
NDA 22-268 Pediatric Page

## REQUEST FOR CONSULTATION

TO (Office/Division): Office of Surveillance and Epidemiology  
(OSE) Attention: Todd Bridges, Team Leader

FROM (Name, Office/Division, and Phone Number of Requestor): Gregory  
DiBernardo, PM/ Joette Meyer, Acting Clinical Team  
Leader, DSPTP/(301) 796-4063

DATE December 22, 2008	IND NO.	NDA NO. 22-268	TYPE OF DOCUMENT Package Insert, Immediate Carton and Container Labels	DATE OF DOCUMENT December 22, 2008
NAME OF DRUG Coartem (proposed) (artemether/lumefantrine)		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG Antimalarial (4050120)	DESIRED COMPLETION DATE December 24, 2008

NAME OF FIRM:

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILTY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

#### IV. DRUG SAFETY

- |   |   |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** The applicant has submitted revised Immediate Carton and Container, Blister Labels to incorporate the recommendations made by DMEPA in its November 7, 2008 Consult Review of these materials. The Division of Special Pathogen and Transplant Products has also revised the Package Insert to reflect the changes suggested by OSE. The following revised materials are attached to this consult request: Immediate Carton and Container Labels, Blister Lables, Revised Package Insert and, e-mails from December 19, 2008 informally requesting your final recommendations.

We would like to request your final recommendations on the Immediate Carton and Container Labels, Blister Labels, and Package Insert at this time.

Please sent your questions to the Project Manager below.

Thank you.

SIGNATURE OF REQUESTOR

Gregory DiBernardo

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

## DiBernardo, Gregory

---

**From:** Meyer, Joette M  
**Sent:** Friday, December 19, 2008 6:25 PM  
**To:** Bridges, Todd; DiBernardo, Gregory  
**Cc:** Albrecht, Renata; Willard, Diana M; Holquist, Carol A; Toyer, Denise P; Francis, Henry  
**Subject:** RE: NDA 22-268-Coartem-Novartis-Revised Immediate Carton and Container Packaging

**Attachments:** 12.19.08 Coartem Label to Novatis.doc

Todd,

Here is the PI.

thanks,  
Joette



12.19.08 Coartem  
Label to Nova...

---

**From:** Bridges, Todd  
**Sent:** Friday, December 19, 2008 5:31 PM  
**To:** DiBernardo, Gregory  
**Cc:** Meyer, Joette M; Albrecht, Renata; Willard, Diana M; Holquist, Carol A; Toyer, Denise P; Bridges, Todd; Francis, Henry  
**Subject:** NDA 22-268-Coartem-Novartis-Revised Immediate Carton and Container Packaging

Greg,

We have made your request a priority this afternoon and have reviewed the labels and labeling as you requested.

In our review dated November 7, 2008, we made recommendations on the container label, carton labeling, and package insert labeling. Our recommended revision to the container label and carton labeling has been incorporated by the Applicant and is acceptable. However, we are unable to determine if our recommendation pertaining to the package insert was incorporated as we did not receive a revised package insert labeling.

In the future, it would be helpful if you could forward any request through the appropriate DMEPA team leader so that workload can be prioritized across the Division. The reviewer which initially completed the review is not always assigned to the follow-up.

Please ensure that we are invited to the lessons learned meeting for this application.

Thank you,  
Todd

---

**From:** DiBernardo, Gregory  
**Sent:** Friday, December 19, 2008 3:56 PM  
**To:** Bridges, Todd  
**Cc:** Meyer, Joette M  
**Subject:** FW: NDA 22-268-Coartem-Novartis-Revised Immediate Carton and Container Packaging  
**Importance:** High

Hello Todd,

I left a message with Denise Baugh regarding this material for NDA 22-268 today, but have not heard back from her. If you could provide an update on this material it would be very helpful as we are now working with a very short time line.

## DiBernardo, Gregory

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**From:** DiBernardo, Gregory  
**Sent:** Friday, December 19, 2008 3:56 PM  
**To:** Bridges, Todd  
**Cc:** Meyer, Joette M  
**Subject:** FW: NDA 22-268-Coartem-Novartis-Revised Immediate Carton and Container Packaging

**Importance:** High

**Attachments:** Coartem 20-120 24 Tablet Label 5001559.pdf; Coartem Ctn 5001755.pdf.zip; Coartem USA 6x1 wallet blister 5001758.pdf.zip; Coartem USA Blister Text 6x1 5001757.pdf

Hello Todd,

I left a message with Denise Baugh regarding this material for NDA 22-268 today, but have not heard back from her. If you could provide an update on this material it would be very helpful as we are now working with a very short time line.

Thank you,  
Gregory

---

**From:** DiBernardo, Gregory  
**Sent:** Thursday, December 18, 2008 11:23 AM  
**To:** Baugh, Denise; Matecka, Dorota M; Pagay, Shrikant N  
**Cc:** Meyer, Joette M  
**Subject:** NDA 22-268-Coartem-Novartis-Revised Immediate Carton and Container Packaging  
**Importance:** High

Hello Everyone,

I have attached the Revised Immediate Carton and Container Packaging for Coartem that Novartis sent in unofficially today. They will be sending in an official submission that addresses the revisions we identified. I will provide a link to the EDR when the Official Submission arrives.

Please let me know if you have any comments or edits for the applicant as soon as possible, please remember our due date of 12/22/08.

Thank you,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063



Coartem 20-120 24  
Tablet Label...



Coartem Ctn  
5001755.pdf.zip (1..



Coartem USA 6x1  
wallet blister...



Coartem USA Blister  
Text 6x1 5...

4 Page(s) Withheld

       Trade Secret / Confidential

X Draft Labeling

       Deliberative Process

Thank you,  
Gregory

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**From:** DiBernardo, Gregory  
**Sent:** Thursday, December 18, 2008 11:23 AM  
**To:** Baugh, Denise; Matecka, Dorota M; Pagay, Shrikant N  
**Cc:** Meyer, Joette M  
**Subject:** NDA 22-268-Coartem-Novartis-Revised Immediate Carton and Container Packaging  
**Importance:** High

Hello Everyone,

I have attached the Revised Immediate Carton and Container Packaging for Coartem that Novartis sent in unofficially today. They will be sending in an official submission that addresses the revisions we identified. I will provide a link to the EDR when the Official Submission arrives.

Please let me know if you have any comments or edits for the applicant as soon as possible, please remember our due date of 12/22/08.

Thank you,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

<< File: Coartem 20-120 24 Tablet Label 5001559.pdf >> << File: Coartem Ctn 5001755.pdf.zip >> << File: Coartem USA 6x1 wallet blister 5001758.pdf.zip >> << File: Coartem USA Blister Text 6x1 5001757.pdf >>

36 Page(s) Withheld

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  X   Draft Labeling

       Deliberative Process

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/s/

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Gregory F DiBernardo  
12/22/2008 05:56:25 PM  
NDA 22-268 OSE Consult Request-Final Recommendations for: PI, Carton,  
Container, & Blister Labels



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**TRANSMITTAL SHEET**

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**DATE:** December 15, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via E-mail	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	
<b>Subject:</b> NDA 22-268-Coartem®-DSPTP Comments regarding Immediate Carton and Container Packaging	

**Total no. of pages including cover:** 3

**Comments: Concurrence**

Joette Meyer, Pharm. D.

Dorota Matecka, Ph.D.

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**Document to be mailed:**       YES       NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our Review team regarding the immediate carton labeling and container labels submitted to this NDA on June 27, 2008.

1. Increase the prominence of the established name commensurate with the prominence of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Please revise the name of the product to include "tablets" in the established name, to read:

COARTEM (artemether/lumefantrine tablets)

or

COARTEM (artemether/lumefantrine) Tablets

If you have any questions regarding this transmittal, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo

12/15/2008 03:14:54 PM

CSO

NDA 22-268 Facsimile Comments regarding Immediate Carton and Container  
Packaging



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**TRANSMITTAL SHEET**

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**DATE:** December 12, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via E-mail	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem®-Statistics Information Request to Clarify Information of excluded subjects and submit case report forms

**Total no. of pages including cover:** 3

**Comments: Concurrence**

Karen Higgins, ScD.

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**Document to be mailed:**             YES             NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our Statistical review team. Due to the timeline involved in this NDA review, please submit these requests officially to the NDA as soon as the information becomes available.

1. Please supply the list of subjects excluded from the evaluable populations as defined in your most recent label (Table 8) along with the reason for their exclusion from the evaluable populations.
2. Additionally, please submit the case report forms for the following subjects:

Study 25: site 3 subject 243, site 3 subject 261

Study 26: site 2 subject 38

Study 2401: site 1 subject 9

Study 2403: site 1 subject 104 and site 1 subject 118

If you have any questions regarding this transmittal, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo  
12/12/2008 09:47:44 AM  
CSO

NDA 22-268 Facsimilie Statistics request to clarify Information of  
excluded subjects and submit case report forms



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

**TRANSMITTAL SHEET**

**DATE:** December 11, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via E-mail	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem®-Clinical Information Request-Study ID numbers for patients 2 months and older

**Total no. of pages including cover:** 4

**Comments:** Concurrence

Sue Lim, M.D.

**Document to be mailed:**                     YES                     NO

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**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1600. Thank you.**

Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following request from our Clinical review team. Please note this request was previously communicated to Novartis, informally via e-mail communication on December 11, 2008 (see attachment below).

Due to the timeline involved in this NDA review, please submit this request officially to the NDA as soon as the information becomes available.

Provide the following information in support of NDA 22-268:

- The study ID numbers for pediatric patient(s) as young as 2 months of age.

If you have any questions regarding this transmittal, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**E-mail Sent on December 11, 2008**

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**From:** DiBernardo, Gregory  
**Sent:** Thursday, December 11, 2008 2:32 PM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** Lim, Sue; Meyer, Joette M  
**Subject:** FW: NDA 22-268-Coartem-Novartis-Clinical Information Request  
**Importance:** High

Hello Susan,

Please be aware of a change in the request from the e-mail below. Our Review team has been able to locate the reports requested in Question #2 below, so please disregard that part of the request. However, please do address in full the request from Question #1.

Thank you and my apologies,  
Gregory

---

**From:** DiBernardo, Gregory  
**Sent:** Thursday, December 11, 2008 1:39 PM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** Lim, Sue; Meyer, Joette M  
**Subject:** NDA 22-268-Coartem-Novartis-Clinical Information Request  
**Importance:** High

Hello Susan,

If you could please address the following requests from our Clinical review team to assist in the review of NDA 22-268. Provide the following information:

1. We are unable to find the pediatric patient(s) as young as 2 months of age. Please provide the Study ID numbers for these patients.
2. Provide the following 6 reports from the Cumulative Safety Report for our review:

Lyell's syndrome reports: **PHRM2002CM01035, PHRM2001CM00621**  
Hypersensitivity: **PHBS2003CM12219, PHBS2002CM04093**  
Angioedema: **PHRM2005SN03372**  
Toxic skin eruption: **PHRM2001FR00576**

We are requesting this information informally now, but it will be followed by an official facsimile. We would appreciate if this information is submitted to the NDA as soon as possible, due to the time lines involved in this NDA review. If you would please send me the information as soon as it becomes available as an e-mail attachment (desk copy). However, please remember to submit your response officially to the NDA via the electronic gateway.

Please let me know if you have any questions.

Thank you,

**Gregory F. DiBernardo**  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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/s/

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Gregory F DiBernardo  
12/11/2008 03:31:14 PM  
CSO  
NDA 22-268 Clinical Facsimile Request Study ID's for 2  
month old and greater

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY ADDENDUM**

DATE: December 4, 2008

TO: Gregory DiBernardo, Regulatory Project Manager  
Elizabeth O'Shaughnessey, M.D., Medical Officer  
Division of Special Pathogen and Transplant Products

FROM: Susan D. Thompson, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

THROUGH: Joseph Salewski  
Deputy Division Director  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-268

APPLICANT: Novartis Pharmaceutical Corporation

DRUG: Coartem<sup>®</sup> (artemether/lumefantrine)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum*

CONSULTATION REQUEST DATE: December 12, 2008

DIVISION ACTION GOAL DATE: December 23, 2008

PDUFA DATE: December 27, 2008

## I. BACKGROUND:

This CIS Addendum is submitted to supplement the CIS for Coartem<sup>®</sup> entered into DFS on November 3, 2008. Coartem<sup>®</sup> (co-artemether; artemether-lumefantrine) is a combination of 20 mg artemether and 120 mg lumefantrine. Co-artemether was originally developed by the Academy of Military Medical Sciences in Beijing, China, and a different formulation of the combination was registered in China in 1992. Ciba (subsequently Novartis) began further development in collaboration with Chinese partners in 1992, and a regimen of 6 doses of Coartem<sup>®</sup> administered over 60 hours was chosen for development. Coartem<sup>®</sup> is currently approved for the treatment of acute, uncomplicated falciparum malaria in adults and pediatric patients with a body weight of  $\geq 5$  kg in the majority of the 83 countries in Africa, Asia, Europe, and Latin America. The Office of Orphan Products Development granted orphan drug designation to Coartem<sup>®</sup> in August, 2007, and Priority Review was granted on August 5, 2008. The PDUFA date for this NDA is December 27, 2008, and an Advisory Committee will review the Coartem<sup>®</sup> application on December 3, 2008. DSI requested foreign inspections of 7 sites (including 2 sites with the same Principal Investigator) on July 25, 2008 and of the sponsor Novartis in Basel, Switzerland on September 5, 2008. This CIS Addendum will provide information which has become available since completion of the CIS on November 3, 2008. Please see the original CIS for further background, including outlines of the protocols audited and a brief summary of study results.

## II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects	Inspection Date	Interim/Final Classification
Jiao Xiu-Qing, M.D. (retired) Contact at site = Dr. Jingyan Wang Institute of Microbiology and Epidemiology, The Academy of Military Medical Sciences, No. 20 Fengtai East Street, Beijing 100071, China Tel.: +86 10 66948546, or +86 13611183711 FAX: +86 10 63813346 E-mail: wangjy@nic.bmi.ac.cn	Protocol A023: 153	11/10-11/21/08	NAI/Pending
Jiao Xiu-Qing, M.D. (retired) Contact at site = Dr. Jingyan Wang Institute of Microbiology and Epidemiology, The Academy of Military Medical Sciences, No. 20 Fengtai East Street, Beijing 100071, China Tel.: +86 10 66948546, or +86 13611183711 FAX: +86 10 63813346 E-mail: wangjy@nic.bmi.ac.cn	Protocol ABOM2: 157	11/10-11/21/08	NAI/Pending

Dr. Sornchai Looareesuwan* (Deceased) Faculty of Tropical Medicine, Mahidol University 420/6 Rajavithree Road, Rajathewee, Bangkok 10400, Thailand Tel.: +66 2 354 9159 FAX: +66 2 354 9158 E-mail: <a href="mailto:tmsks@mahidol.ac.th">tmsks@mahidol.ac.th</a>	Protocol A025: 100 Protocol A026: 28 Protocol A028: 219	10/20-10/24/08, 10/27-10/28/08	VAI/Pending
Prof. Francois Nosten Shoklo Malaria Research Unit 68/30 Baan Tung Road, PO Box 46 Mae Sot Tak 63110 Thailand Tel.: +66 55 545 021 Mob. Tel.: +668 1881 3350 FAX: +66 55 5545 020 E-mail: <a href="mailto:francois@tropmedres.ac">francois@tropmedres.ac</a>	Protocol A025: 259 Protocol A026: 172	10/13-10/31/08	VAI/Pending
Dr. Michael Makanga Kenya Medical Research Institute KEMRI Kilifi, Kenya Current contact info: Francie van Zijl Drive, Parow PO Box 19070, Tygerberg 7505 Cape Town, South Africa Tel.: +27 21 938 0509 FAX: +27 219380569 E-mail: <a href="mailto:Makanga@edctp.org">Makanga@edctp.org</a>	Protocol B2403: 107	10/13-10/17/08	VAI/Pending
Prof. Zul Premji Muhimbili University United Nations Road Box 65011 Dar es salaam, Tanzania Tel.: +255 754304468 FAX: +255 22 2150465	Protocol B2403: 100	10/20-10/24/08	VAI/Pending
Dr. Salim Abdulla Ifakara Health Research and Development Centre Dar es salaam, Tanzania Current contact info: Bagamoyo Research and Trainig Unit Ifakara Health Research and Development Centre, Bagamoyo Branch, PO Box 74 Bagamoyo, Tanzania Tel.: +255 23 244 0064 Mob. Tel.: +255754744555 FAX: none E-mail: <a href="mailto:sabdulla@ihi.or.tz">sabdulla@ihi.or.tz</a>	Protocol A2303: 240	10/27/08 – 11/5/08	VAI/Pending
Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel – Switzerland Contact: Matthew Stoudemayer (Novartis East Hanover, New Jersey) Phone: (862) 778-0291 Fax: (973) 781-3132	Protocol A023 Protocol ABOM2 Protocol A025 Protocol A026 Protocol A028 Protocol B2403 Protocol A2303	10/27/08-11/7/08	VAI/Pending

\*The records for this site were moved to a (b) (4)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

**1. Dr. Sornchai Looareesuwan\***

**Faculty of Tropical Medicine**

**Mahidol University**

**420/6 Rajavithree Road**

**Bangkok, 10400 Thailand**

**\*Contact information: Dr. Srivicha Krudsood, Clinical Investigator at the same address/site; Dr. Looareesuwan is deceased.**

**PLEASE SEE FULL SUMMARY IN THE CIS COMPLETED NOVEMBER 11, 2008. UPDATED INFORMATION IS PROVIDED BELOW.**

- a. What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. The inspectors report that the total number of subjects screened at the site cannot be determined since screening was performed as part of the hospital admission process, with the study staff only confirming that a subject was appropriate for the study. For Study 025, 114 subjects were enrolled; for Study 026, 12 subjects were enrolled; and for Study 028, 79 subjects were enrolled. The records of 17 subjects were reviewed by the inspectors for Study 025, 12 records for Study 026, and 79 records for Study 028. (b) (4)

The observations noted are based on preliminary communications with the FDA field investigators, the Form FDA 483, (b) (4). A second inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR with exhibits. There were no limitations to the inspection.

- b. General observations/commentary:** Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60 and did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b). (See CIS dated November 3, 2008 for details.)

(b) (4)

(b) (4)

- c. **Assessment of data integrity:** Review (b) (4) does not result in a change in the previous conclusion regarding data integrity at Dr. Looareesuwan's site: although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies. The data appear acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum*.

**2. Dr. Francis Nosten**  
**Shoklo Malaria Research Unit**  
**68/30 Baan Tung Road, PO Box 46**  
**Mae Sot Tak, 63110 Thailand**

**PLEASE SEE FULL SUMMARY IN THE CIS COMPLETED NOVEMBER 11, 2008. UPDATED INFORMATION IS PROVIDED BELOW.**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. The inspectors report that the investigators did a prescreen and then entered subjects if qualified. There is no record of anyone failing screening. For Study 025, 259 subjects were screened and enrolled; for Study 026, 172 subjects were screened and enrolled. For Study 025, 206 subjects completed the study and 147 subjects completed Study 026. The records of 87 subjects were reviewed by the inspectors for Study 025 and 60 records were reviewed for Study 026. (b) (4)  
The observations noted are based on preliminary communications with the FDA field investigators, the Form FDA 483 (b) (4). A second inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the

investigational plan, in violation of 21 CFR 312.60 and did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b). (See **CIS dated November 3, 2008 for details.**)

During the inspection of Novartis (See Item 7 below) it was noted that the Principal Investigator Dr. Nosten for clinical trial A2412 of Coartem<sup>®</sup> did not have a valid license to practice medicine in Thailand at the time of that study and had not received IRB approval from the government of Thailand; he did, however, obtain IRB approval from Mihadol Hospital. He proceeded with enrollment despite being told not to start the study by Novartis. This study was conducted several years after Studies 025 and 026. (b) (4)

[Redacted text block]

(b) (4)  
[Redacted text block]

[Redacted text block]

- c. **Assessment of data integrity:** Review (b) (4) does not result in a change in the previous conclusion regarding data integrity at Dr. Nosten's site: although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies. The data appear acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum*.

**3. Dr. Michael Makanga**  
**Kenya Medical Research Institute**  
**KEMRI**  
**Kilifi, Kenya**

**Current contact information: Francie van Zijl Drive, Parow, PO Box 19070, Tygerberg 7505, Cape Town, South Africa**

**PLEASE SEE FULL SUMMARY IN THE CIS COMPLETED NOVEMBER 11, 2008. UPDATED INFORMATION.**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. For Study 2403, 456 subjects were screened and 107 subjects were enrolled, and 104 subjects completed the study; 3 subjects discontinued the study prior to conclusion. The records of 28 subjects were reviewed by the inspector, including subjects in all three study groups. The informed consent document was reviewed for all 107 subjects. (b) (4)

(b) (4)  
The observations noted are based on preliminary communications with the FDA field investigator, the Form FDA 483, (b) (4), and Dr. Makenga's written response to the Form FDA 483. A second inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR with exhibits. There were no limitations to the inspection.

- b. **General observations/commentary:** Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspector considered that there was no evidence of fraud and that Dr. Makenga appeared to be a dedicated and knowledgeable researcher.

However, the inspection documented that Dr. Makenga did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b). (See CIS dated November 3, 2008 for details.) A response from Dr. Makenga to the Form FDA 483 observations dated November 20, 2008 was received. The letter provided explanations for some of the inspector's observations; however,

information to contradict the deficiencies noted on the Form FDA 483 was not presented. No new information was contained in the draft EIR.

- c. **Assessment of data integrity:** Review of (b) (4) Dr Makenga's response to the Form FDA 483 does not result in a change in the previous conclusion regarding data integrity at Dr. Makenga's site: although recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum*.

**4. Professor Zulfigarall Premji**  
**Muhimbili University**  
**United Nations Road**  
**Box 65011**  
**Dar es salaam, Tanzania**

**PLEASE SEE FULL SUMMARY IN THE CIS DATED NOVEMBER 3, 2008. NO ADDITIONAL INFORMATION IS AVAILABLE.**

**5. Dr. Salim Abdulla**  
**Muhimbili University**  
**United Nations Road**  
**Box 65011**  
**Dar es salaam, Tanzania**

- a. **What was inspected:** The inspector reports that the screening log was incomplete, and that it fails to include 10 subjects who were enrolled; it was not possible to determine how many patients were not included that were screened and excluded. The site enrolled 242 subjects; two were screening failures, so 240 completed the study. Efficacy endpoint data was checked for approximately 190 of the subjects. Also, the informed consent documents of 80 subjects were checked. (b) (4)  
The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. A second inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR and exhibits. There were no limitations to the inspection.
- b. **General observations/commentary:** Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that Dr. Abdulla did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b), as follows.

1. The screening and enrollment log for the study was incomplete in that it failed to include screening data for all patients screened. The screening log lacked screening and enrollment data for ten subjects that were enrolled in the study (Subjects #018, 019, 020, 192, 193, 194, 195, 196, 197, and 198).
2. Discrepancies were noted between the parasite density counts calculated from data in source documents and the density counts reported in the sponsor's database. For example, for study Subject #124, source data indicates the parasite density count at the 8-hr interval was 212; however, no value for parasite density was reported in the CRF, and no value appeared in the sponsor's database.
3. The "Preparation and Dispensing Log for Coartem<sup>®</sup>", containing source data for the date and time of test article preparation and identification of the persons that prepared and administered the test article, was incomplete and/or inaccurate as follows:
  - i. It failed to include any data for at least 21 study subjects. In addition, for over 500 dosings recorded in the log, it failed to include identification of the person that prepared the test article.
  - ii. The log suffered water damage and contained several pages of data that appears to have been manipulated in some fashion, with no documented explanation in study records.

*Medical Officer's Comment: According to site representatives, the log was affected by flooding. Examination of faxed pages from the log appears to show "tracing" of data, rather than intentional alteration of underlying information.*
4. Study records did not identify the person that assigned randomization numbers to study subjects.
5. Written informed consent for Subject #29 was not signed by the patient or guardian prior to the minor child being dosed with the test article.

In addition, after transmission of the Form FDA 483, the inspector sent an email stating that study records did not document whether dispersible or conventional Coartem<sup>®</sup> tablets were prepared for subject administration, and noting that the pharmacist recognized whether tablets were dispersible or conventional, and prepared them appropriately. We requested that copies of the Pharmacy Preparation and Dispensing log be faxed to us for further examination. On examination of photos of the blister packs, it was apparent that there was a 2-part label containing the randomization number which was to be affixed to the source document. In addition, blister packs of dispersible and conventional tablets were visually distinctive. Therefore, verification of which formulation a given subject received could be accomplished by comparison of the randomization number with the master records kept by Novartis. The initial concern that the form of Coartem<sup>®</sup> administered to a

given subject could not be verified was not validated. Although clearly a regulatory violation, there is no evidence that data integrity was impacted.

A response to the Form FDA 483 from Dr. Abdulla dated November 15, 2008 was received. Dr. Abdulla claims that the Pharmacy Preparation and Dispensing Log was in fact not a source document, and was not required in the protocol or in the specified standard operating procedures (SOPs) of the study at the site. The rest of the deficiencies were acknowledged.

- c. Assessment of data integrity:** Review of the inspector's additional information as well as Dr. Abdulla's response does not result in a change in the previous conclusion regarding data integrity at Dr. Abdulla's site: although protocol and record keeping violations occurred at Dr. Abdulla's site, it is unlikely that these errors will impact the final outcome of the study. It also does not appear that the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies. (b) (4)
- The observations noted are based on preliminary communications with the FDA field investigator, the Form FDA 483, and Dr. Abdulla's written response. There were no limitations to the inspection.

**6. Dr. Jiao Xiu-Qing, M.D.**  
**Institute of Microbiology and Epidemiology**  
**The Academy of Military Medical Sciences, No. 20**  
**Fengtai East Street, Beijing 100071, China**

- a. What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. The total number of subjects screened cannot be determined since screening was performed at Nindao Farm's Hospital and then subjects sent to the study site, Naval Hospital 425 on Nan Dao Island if they fulfilled study criteria. For Study ABMO2, 157 subjects were enrolled; for Study A023, 153 subjects were enrolled. The records of 39 subjects were reviewed by the inspectors for Study ABMO2 for consent compliance, plus 60 others were reviewed; 41 records were reviewed for Study 023. (b) (4)
- The observations noted are based on preliminary communications with the FDA field investigators; no Form FDA 483 was issued. A second inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR with exhibits. There were no limitations to the inspection.
- b. General observations/commentary:** Generally, the investigator was found to have executed the study adequately, and no Form FDA 483 was issued. The inspector noted that six Informed Consent documents were missing from Study ABMO2 records, and an unspecified number from Study A023. However, the inspector stated that the required record retention time had been exceeded, such that no Form FDA 483 was issued.

- c. **Assessment of data integrity:** The data from Dr. Xiu-Qing’s site appears acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum*.

7. **Sponsor/Monitor/CRO**

**Novartis Pharma AG**

**Lichtstrasse 35**

**CH-4056 Basel – Switzerland**

**Contact: Matthew Stoudemayer (Novartis East Hanover, New Jersey)**

- a. **What was inspected:** The FDA investigator reviewed Novartis procedures and records for protocols A023, ABMO2, A025, A026, A028, A2401, A2303, and B2303. The inspection began on October 27, 2008 and was concluded on November 7, 2008. The inspector reviewed the Organization and Personnel, Site Selection, Monitoring Procedures and Activities, Record Retention, as well as Test Article Integrity and Accountability records of the eight pivotal studies submitted for this NDA (all of the studies inspected as well as A2401). (b) (4)

The observations noted are based on preliminary communications with the FDA field investigator. (b) (4)

There were no limitations to the inspection.

- b. **General observations/commentary:** The inspector encountered technical difficulties at the conclusion of the inspection. Because of these difficulties, he chose not to issue a Form FDA 483, but instead communicated the deficiencies noted during the inspection to Novartis representatives. His intention was to issue the Form FDA 483 at a later time; however, his supervisor decided that no Form FDA 483 could be issued once the inspector had departed the site. The following information was sent to this reviewer, with the statement that these items would have been included on a Form FDA 483:

1. Did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation [21 CFR 312.62(b)
  - i. Studies that were either blinded or had a blinded arm (A025, ABMO2, and A023) were provided a sealed envelope containing a “code break” to be used in the event of a serious adverse event. Code breaks for all three sites could not be located in the firm’s archived master trial folder.
  - ii. Packaging release documentation identifying the Lot/Batch number of the study medication Coartem® for Subjects #01-50 for Study ABMO2 were not retained.
  - iii. Packaging/labeling records for Study A025, Lot 502, for patients #1-120 were not retained.
  - iv. Certificate of Return Destruction record for Studies A023 were not completed or were lost.
  - v. The sponsor did not have a study specific protocol or SOP for the packaging, labeling, and release of the study medication for Study ABMO2.

2. Did not adhere to the investigational plan [21 CFR 312.60]
    - i. An Initiation Visit for Study A026 Site 02 was not conducted.
    - ii. Closeout Site visit Monitoring Reports A025 and A023 were not conducted and did not verify the existence or integrity of the code break envelopes
    - iii. The Closeout Report for Study B2303 (Site 301) was issued prior to the resolution of unresolved issues noted in the report.
    - iv. The protocol for ABMO2 was not signed by the Statistician prior to the enrollment of the first patient.
  3. Failure to select only investigators qualified by training and experience as appropriate experts to investigate the drug [21 CFR 312.53]
    - i. The process for Clinical Investigator selection was deficient in that an inadequately credentialed principal investigator was supplied with study medication in Study A2412 and was not prevented from initiating the study trial prior to governmental approval.
  4. Discussion Point
    - i. Study medication was given to the principal investigators in Study A2303 at all three sites, for distribution in humanitarian use, while the Drug disposition and site closure SOPs call for the return and destruction of study medication.
- c. **Assessment of data integrity:** The data collected and maintained at the sponsor's site, as it pertains to the eight clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348.810 appear consistent with that submitted to the agency as part of and in support of NDA 22-268. It is unlikely that the deficiencies identified above will impact data integrity or the final outcomes of the studies. After the EIR is received, a second inspection summary addendum will be generated if necessary.

#### IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. There were no significant regulatory violations documented at Dr. Xiu-Qing's site for Protocols A023 and ABMO2. The inspections documented minor regulatory violations at the sites of Drs. Looareesuwana, Nosten, Makenga, Premji, and Abdulla regarding protocol and recordkeeping violations. In general, the studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

The data collected and maintained at the sponsor's site, as it pertains to the eight clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348.810, appear consistent with that submitted to the agency as part of and in support of NDA 22-268.

Follow-Up Actions: The observations noted above for Drs. Makenga, Premji, Abdulla, and Xiu-Qing are based on preliminary communications with the FDA field investigators and

the Form FDA 483, when issued. (b) (4)

. A second inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

*{See appended electronic signature page}*

Susan D. Thompson, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Joseph Salewski  
Deputy Division Director  
Division of Scientific Investigations

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/s/

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Susan Thompson  
12/8/2008 02:31:25 PM  
MEDICAL OFFICER

Joseph Salewski  
12/10/2008 04:12:02 PM  
CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**TRANSMITTAL SHEET**

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**DATE:** December 5, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via E-mail	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem®-Clinical and Statistics Information Request

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**Total no. of pages including cover:** 4

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**Comments: Concurrence**

Karen Higgins, ScD.

Joette Meyer, Pharm. D.

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**Document to be mailed:**  YES  NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our review teams. Please note these requests were previously communicated to Novartis. The Statistics request in #1 below was informally requested via e-mail communication on December 1, 2008 (see attachment below); while the Clinical request in #2 below was listed as question # 9 in an official facsimile request dated October 10, 2008. Due to the timeline involved in this NDA review, please submit these requests officially to the NDA as soon as the information becomes available.

1. If you could please clarify the following information from your 11/26/08 submission it would be very helpful for our Statistics review team. In study A030 (also referred to as 1030), this protocol describes an uncontrolled trial in Vietnam. However, the study report under 1030.pdf is of a controlled trial of Coartem vs. Artesunate-Mefloquine in Vietnam.
  - a. Please clarify if you have an updated protocol which includes the control arm or state if this a completely different study.
  - b. If it is a completely different study, we would like you to submit the protocol for the study whose study report was submitted on 4/18/08 under 1030.pdf?
2. Please provide a brief written discussion of the clinical significance of a rapid reduction in parasite counts caused by artemether in the treatment of malaria. Since Coartem is a combination product, it is important to demonstrate the contribution of each of the components to the overall efficacy of the regimen, as you have done in Studies A023 and ABMO2. In these studies you have shown that Coartem is superior to lumefantrine alone in terms of the early endpoints (i.e., parasite clearance time and parasite reduction at 24 hours). However, Coartem was not significantly different from lumefantrine at the 28-day visit. In Study ABMO2 you have shown that Coartem is similar to artemether in terms of these same early endpoints. Therefore, please include a rationale why the early reduction in parasite count seen with Coartem, and attributed to artemether, is clinically important in treating malaria.

If you have any questions regarding this transmittal, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

### E-mail Sent on December 1, 2008

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**From:** DiBernardo, Gregory  
**Sent:** Monday, December 01, 2008 4:59 PM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** 'paula.rinaldi@novartis.com'; Higgins, Karen M  
**Subject:** NDA 22-268-Coartem-Novartis-Please Clarify Study A030  
**Importance:** High

Hello Susan,

If you could please clarify the following information from your 11/26/08 submission it would be very helpful for our review team. For study A030 (also referred to as 1030), this protocol describes an uncontrolled trial in Vietnam. However, the study report under 1030.pdf is of a controlled trial of Coartem vs. Artesunate-Mefloquine in Vietnam.

- Please clarify if you have an updated protocol which includes the control arm or is this a completely different study.
- If it is a completely different study, we would like you to submit the protocol for the study whose study report was submitted on 4/18/08 under 1030.pdf?

We are requesting this information informally now, but it will be followed by an official facsimile. We would appreciate if this information is submitted to the NDA as soon as possible, due to the time lines involved in this NDA review. If you would please send me the information as soon as it becomes available as an e-mail attachment (desk copy). However, please remember to submit your response officially to the NDA via the electronic gateway.

Please let me know if you have any questions.

Thank you,

**Gregory F. DiBernardo**  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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/s/

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Gregory F DiBernardo  
12/5/2008 11:36:14 AM  
CSO  
NDA 22-268 Clinical and Statistics Information Request



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: James L. DeMartino, Ph.D.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Dr. DeMartino:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Coartem (artemether 20 mg/lumefantrine 120 mg) Tablets.

We have received your request for fast track designation and your request for step-wise submission of sections of a New Drug Application (NDA) under section 506 of the Act. Please note the following identifying data.

Name of Drug:	Coartem (artemether 20 mg/lumefantrine 120 mg) Tablets
Proposed Indication:	Treatment of malaria
Date of submission requesting step-wise submission of NDA:	October 30, 2007
Date of Receipt of submission requesting step-wise submission of NDA:	November 2, 2007
Date of submission of fast track designation request:	November 15, 2007
Date of receipt of submission for fast track designation:	November 16, 2007

We are reviewing your submissions and we will respond to you within 60 days of the above date of receipt of your request for fast track designation.

If you have any questions, please call me at 301-796-1600.

Sincerely,

*{See appended electronic signature page}*

Diana Willard  
Chief, Project Management Staff  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Diana Willard

11/26/2007 05:09:32 PM

NDA 22-268 Acknowledgement of Rolling Review Submission/Request for Fast  
Track Designation



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**TRANSMITTAL SHEET**

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**DATE:** November 19, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via E-mail	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem®-Clinical and Statistics Information Request Time to Parasite Clearance Study 026

**Total no. of pages including cover:** 5

**Comments: Concurrence**

Xianbin Li, Ph.D.

Elizabeth O'Shaughnessy, M.D.

Karen Higgins, ScD.

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**Document to be mailed:**  YES  NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our review team. Please note these requests were originally communicated informally to Novartis via e-mail communication on November 18, 2008 (see attachment below) and clarification of these requests were sent on November 19, 2008 via e-mail communication (see attachment below). Due to the timeline involved in this NDA review, please submit these requests officially to the NDA as soon as the information becomes available.

- Please calculate and submit the time to parasite clearance in hours for each subject in Study 026.
- Please submit the raw data used to calculate the time to parasite clearance for each subject in study 026, if not submitted previously.

Please see the following information for clarification of the requests listed above:

- We are interested in a variable, one line per subject, which contains parasite clearance time for subjects in study 026. A small electronic data set containing subject ID along with PCT would be adequate. Note that we understand that parasite count was not measured as often in this study as it was for the other key studies and that the data set A\_PC contains parasite count over time for all subjects. We have used the variable ASEX1N for parasite count and RVIS1N for time and were able to duplicate the results for the median that you have presented on page 46 of your background document.
- Please discuss the reason for using the variable RVIS1N rather than the variable HRS\_1N in order to calculate parasite clearance time for this study, since HRS\_1N appears to be the actual time that the parasite count was measured as opposed to rounding time to a 24 hour time period as was done for RVIS1N.

If you have any questions regarding this transmittal, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

### E-mail Sent on November 19, 2008

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**From:** DiBernardo, Gregory  
**Sent:** Wednesday, November 19, 2008 3:24 PM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** Higgins, Karen M; Li, Xianbin; Meyer, Joette M; O'Shaughnessy, Elizabeth  
**Subject:** FW: NDA 22-268-Coartem-Novartis Follow-up RE: Parasite Clearance data  
**Importance:** High

Hello Susan,

As a follow-up to our telephone calls earlier today, I am providing the clarifying comment to the request in my email below. My email below was in response to your email of 11/14/08. I will incorporate this clarifying comment into the official facsimile request for this information. Please let me know if you have any further questions.

#### **FDA Clarification:**

**We are interested in a variable, one line per subject, which contains parasite clearance time for subjects in study 026. A small electronic data set containing subject ID along with PCT would be adequate. Note that we understand that parasite count was not measured as often in this study as it was for the other key studies and that the data set A\_PC contains parasite count over time for all subjects. We have used the variable ASEX1N for parasite count and RVIS1N for time and were able to duplicate the results for the median that you have presented on page 46 of your background document.**

**Please discuss the reason for using the variable RVIS1N rather than the variable HRS\_1N in order to calculate parasite clearance time for this study, since HRS\_1N appears to be the actual time that the parasite count was measured as opposed to rounding time to a 24 hour time period as was done for RVIS1N.**

Thank you,  
Gregory

### E-mail Sent November 18, 2008

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**From:** DiBernardo, Gregory  
**Sent:** Tuesday, November 18, 2008 2:51 PM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** Meyer, Joette M; O'Shaughnessy, Elizabeth; Higgins, Karen M; Li, Xianbin  
**Subject:** NDA 22-268-Coartem-Novartis Follow-up RE: Parasite Clearance data

Hello Susan,

As a follow-up to our telephone conversation earlier today, our review team would like the following information submitted to the NDA. I have added in our comment as reply to your email from 11/14/08, as requested. We are requesting this information informally now, but it will be followed by an official fax. We would appreciate if this information is submitted to the NDA as soon as possible, due to the time lines involved in this NDA review. If you would please send me the information as soon as it becomes available as an email attachment (desk copy).

Please calculate and submit the time to parasite clearance in hours for each subject in Study 026. Please submit the raw data used to calculate the time to parasite clearance for each subject in study 026.

Please let me know if you have any other questions.

Thank you,  
Gregory

---

**From:** susan.kummerer@novartis.com [mailto:susan.kummerer@novartis.com]

**Sent:** Friday, November 14, 2008 1:17 PM

**To:** DiBernardo, Gregory

**Subject:** Parasite Clearance data

Dear Gregory,

I have highlighted in red where I believe the information you are looking for is located. Study A026 was submitted on February 27, 2008.

Please let me know if this is what you need before we proceed to a final drafting.

Parasite clearance time for all patients (including patients from study A026) can be found in CRT dataset A\_EFF, variables

PCT\_1N - Parasite clearance time (hrs)

PCTC\_1C - PCT censored (coded)

This dataset was used for the Kaplan Meier analyses of parasite clearance time presented in our advisory committee briefing book.

According to the schedule used in this study, blood microscopy for parasites was to be assessed at the following timepoints:

Pre-treatment - Day 0 (Hr 0)

Day 2 - Hr 24

Day 3 - Hr 48

Day 4 - Hr 72

Day 5\*

Day 6\*

Day 8

Day 15

Day 22

Day 29

\* only if clearance not yet achieved

Regards,

Susan

In the A026 Clinical Study Report, time to parasite clearance was not an endpoint derived or analyzed. No Kaplan Meier analysis for time to parasite clearance was conducted but the number and percent of patients with negative slides at days 2, 3, or 4 were tabulated for the clinical study report. This accounts for the sparse schedule of blood microscopy used in this study which does not support the assessment of time to parasite clearance.

However for the pooled efficacy data analysis supporting the clinical overview, the time to parasite clearance was calculated also for this study. This variable was not derived based on the actual time reported for the blood microscopy, but rather based on the day of microscopy. As a consequence all parasite clearance time values are multiples of 24 hours.

All parasite density measurements reported for a patient can be found in CRT dataset A\_PC. This dataset contains variables for parasite counts as well for the exact hours since 1st intake of study drug. Please refer to the CTR dataset A\_PC, variables

HRS\_1N - Hours since first dose

ASEX1N - P. falc. asexual form count

ASEXP1C - P. falc. asexual form - present (coded)

ASEXP1A - P. falc. asexual form - present (Decode)

Susan Kummerer

Novartis Pharmaceuticals Corporation

PH

USEH

Novartis Pharmaceuticals Corporation

One Health Plaza

East Hanover, NJ 07936-1080

USA

Phone: +1 8627781130

Email : susan.kummerer@novartis.com

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/s/

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Gregory F DiBernardo

11/19/2008 05:14:34 PM

CSO

NDA 22-268 Clinical and Statistics Information Request Time to  
Parasite Clearance Study 026



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**TRANSMITTAL SHEET**

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**DATE:** November 12, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via Email	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

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**Subject:** NDA 22-268-Coartem®-Clinical Information Request-from 11/07/08 Brief Teleconference

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**Total no. of pages including cover:** 3

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**Comments: Concurrence**  
Joette Meyer, Pharm. D.

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**Document to be mailed:**                     YES                     NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our review team. Please note some of these requests were originally communicated verbally to Novartis during a brief teleconference on November 7, 2008.

- During a Face to Face presentation involving Novartis and the Division of Special Pathogen and Transplant Products (DSPTP) on October 15, 2008 it was requested by the DSPTP that data and comparisons on Fever Clearance Time in children be included as part of your Briefing Book for the December 3, 2008 Advisory Meeting for NDA 22-268. After reviewing your Final Briefing Book submitted to the NDA on October 30, 2008, it was identified that this material had been omitted. Please submit an analysis of Fever Clearance Time in children, which accounts for use of antipyretics. Please include a discussion of the effects of antipyretics on fever in patients with malaria.
- In preparation for your Advisory Committee Presentation the DSPTP would like you to include a slide and discussion of the data in the NDA which supports the use of Coartem® in adult patients  $\geq 70$ kg, as this population is thought to be more representative of the U.S. population.
- According to the final study report and Clinical Overview section of the NDA, both Formulation F4 and F5 were used in Study A2401. However, during an e-mail exchange and telephone conversation with John Cutt on November 6 and 7, 2008, he indicated that an error had been made and only Formulation F.4 was used in the study. Please submit an official and signed statement to the NDA that explains the error and clearly identifies what formulation was used in Study A2401.

Please note that we have an additional request that was not communicated during the teleconference on November 7, 2008, but has been incorporated into this facsimile request to expedite its communication.

In your Clinical Overview section of the NDA you discuss the criteria you used for classifying a patient as having mild, moderate, or severe hepatic or renal impairment (page 90, section 4.5.1). You also discuss the results from these subgroup analyses in terms of efficacy (page 93, for adults) and safety (page 183, for adults) for adults and children. However, you have not provided the corresponding data tables, to support your conclusions.

- Please submit tables of efficacy and safety results for adult ( $> 16$  years) and pediatric ( $\leq 16$  years) patients with hepatic (mild, moderate and severe) or renal (mild, moderate, and severe) impairment.

If you have any questions regarding this transmittal, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Gregory F DiBernardo

11/12/2008 01:33:41 PM

CSO

NDA 22-268-Clinical Information Request from 11/07/08 Brief Teleconference

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: November 3, 2008

TO: Gregory DiBernardo, Regulatory Project Manager  
Elizabeth O'Shaughnessey, M.D., Medical Officer  
Division of Special Pathogen and Transplant Products

FROM: Susan D. Thompson, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-268

APPLICANT: Novartis Pharmaceutical Corporation

DRUG: Coartem<sup>®</sup> (artemether/lumefantrine)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: 1. Treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum*

CONSULTATION REQUEST DATE: November 4, 2008 deadline for Advisory Committee Briefing Package

DIVISION ACTION GOAL DATE: December 23, 2008

PDUFA DATE: December 27, 2008

## I. BACKGROUND:

Coartem<sup>®</sup> (co-artemether; artemether-lumefantrine) is a combination of 20 mg artemether (an artemisinin derivative) and 120 mg lumefantrine (a racemic mixture of a synthetic racemic fluorine derivative formerly known as benflumetol). Coartemether acts as a blood schizonticide; its components show complementary pharmacokinetics and have dissimilar modes of action providing synergistic activity against *Plasmodium falciparum*. Artemisinin derivatives, such as artemether, are among the most effective antimalarials, and are active against all *Plasmodium* species that infect humans, with a more rapid rate of parasite clearance than any other antimalarials. Combination with other antimalarials with slower elimination rates, such as lumefantrine, allows shorter course of treatment (3 days) to be effective. Artemether rapidly reduces parasitemia and the long-acting lumefantrine eliminates residual parasites. The most common adverse events associated with Coartem<sup>®</sup> include central nervous system reactions (headache and dizziness) and gastrointestinal reactions (abdominal pain and nausea). Other common adverse events include central nervous system (sleep disorders), gastrointestinal (diarrhea, vomiting and nausea), cardiovascular (palpitations), dermatologic (pruritus and rash), respiratory (cough), and musculoskeletal (arthralgia and myalgia). Combination antimalarial therapy is now recommended by the World Health Organization (WHO) for increased efficacy and minimization of the risk of treatment failure due to development of drug resistance during treatment.

Up to 500 million cases of *P. falciparum* malaria per year are reported globally, resulting in over 1.2 million deaths each year. Over 90% of cases of malaria occur in Africa, and the patients most at risk of morbidity and mortality are small children. *P. falciparum* malaria has the highest morbidity and mortality when compared with *Plasmodium vivax*, *Plasmodium ovale*, or *Plasmodium malariae*. In the United States, malaria is primarily a problem for travelers to endemic areas.

Co-artemether was originally developed by the Academy of Military Medical Sciences in Beijing, China. A different formulation of the combination was registered in China in 1992. Ciba (subsequently Novartis) began further development in collaboration with Chinese partners in 1992. Earlier studies evaluated the 4-dose regimen of co-artemether: one dose at the time of diagnosis and further doses at 8, 24, and 48 hours thereafter, with 1 to 4 tablets per dose according to body weight. However, the 4-dose regimen did not provide the expected efficacy and further studies using 6-dose regimens were performed. Two six-dose regimens were initially evaluated, with doses given at 0, 8, 24, 36, 48, and 60 hours or at 0, 8, 24, 48, 72, and 96 hours. The regimen of 6 doses given over 60 hours was chosen for further development and registration. The initial registration of co-artemether was in 1998 and 1999. It is now approved for acute, uncomplicated falciparum malaria in adults and pediatric patients with a body weight of  $\geq 5$  kg in the majority of the 83 countries in Africa, Asia, Europe, and Latin America. The 6-dose regimen replaced the 4-dose regimen; <sup>(b) (4)</sup> patients have been treated with co-artemether since the first approval of the drug (non-U.S.) in 1998. It is not currently approved in the United States. All studies performed since the collaboration between Ciba/Novartis and the Chinese partners (from 1992) were conducted according to international GCP guidelines and Ciba/Novartis SOPs, and comply with the Declaration of Helsinki and its

recent revisions. Studies performed by the AMMS, Beijing, China, for the registration of lumefantrine and co-artemether were not totally compliant with GCP.

Key studies included in this submission are those that provide evidence in support of registration of the 6-dose regimen of co-artemether. These include two studies with the 4-dose regimen comparing the combination product with its components, studies ABMO2 and A023, and six studies providing substantial evidence of the efficacy and safety of the 6-dose regimen. These were studies A025, A026, A028, A2401, A2403, and B2303. The results for these studies were submitted on a rolling basis to the NDA. No placebo-controlled studies were performed for ethical reasons. The Office of Orphan Products Development granted orphan drug designation to Coartem<sup>®</sup> in August, 2007, and Fast Track Designation was granted on January 14, 2008. The sponsor has requested Priority Review for this application. The sponsor has requested the indication for Coartem<sup>®</sup> of treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum*. Brief synopses of the protocols which the division has requested to be inspected are given below.

**Protocol A023:** A randomized, parallel group, comparative trial of an oral anti-malarial drug combination, co-artemether, and one of its components, benflumetol (2 formulations), given to patients with *Plasmodium falciparum* infection: a combined pharmacokinetic and efficacy trial in China

This single site, single investigator Phase 2 trial was conducted in China, from June, 1996 to November, 1996. The trial was a randomized, parallel group comparative trial of the oral anti-malarial drug combination CGP 56697 (co-artemether) versus lumefantrine alone (tablets and capsules). This study enrolled male or female patients aged 13 years or more, weighing >35 kg; patients with *P. falciparum* asexual parasitemia less than 1,000 or more than 150,000/ $\mu$ L or signs of severe or complicated *P. falciparum* infection were excluded. CGP 56697 was administered as 4 doses of 4 tablets over 48 hours (hours 0, 8, 24, and 48). This regimen corresponds to 480 mg benflumetol (lumefantrine) and 80 mg artemether per dose and a total of 1,920 mg benflumetol and 320 mg artemether per treatment course of CGP56697 or lumefantrine alone. Lumefantrine capsules were given according to the Chinese registered schedule (8 capsules at start, followed 4 capsules each at hours 24, 48, and 72). One capsule contained 100 mg of lumefantrine, thus the total dose was 2,000 mg. Lumefantrine tablets were administered in a 4 dose regimen identical to that used for co-artemether (total lumefantrine dose 1920 mg). During the first 72 hours, patients were monitored for parasites (blood microscopy) and fever at 6 hourly intervals. Thereafter, temperature and blood microscopy were performed once daily until Day 8. After the first week, blood microscopy was performed weekly (Days 8, 15, 22, and 29) and temperature measured daily. If the patient's medical condition indicated reappearance of *P. falciparum* or *P. vivax*, blood film slides were taken daily until resolution. A 12-lead ECG was performed on Day 1, 2, 4, 8, and 29. Hematology (hemoglobin, hematocrit, RBC, WBC with differential, platelets, and reticulocytes), Biochemistry (total bilirubin, alkaline phosphatase, SGOT, SGPT, sodium, potassium, glucose, creatinine, urea, total protein, albumin), and urinalysis (albumin, glucose, bilirubin, blood) studies were performed on Days 1, 2, 4, and 8. Follow-up ended at Day 29.

Efficacy was assessed in terms of time to parasite clearance (PCT), time to fever clearance (FCT), parasite reduction at 24 hours, 28 day parasitological cure rate, and anti-gametocyte activity (clearance of existing gametocytes without the need for further anti-malarials). The protocol states that CGP 56697 was considered more effective if there was a clinically and statistically significant difference between CGP 56697 and benflumetol in PCT or parasite reduction at 24 hours.

#### Brief Summary of Results

The study population consisted of patients 12 to 65 years of age, and 87% were males. Median parasite density at baseline was 11,800 asexual forms/ $\mu$ L for the co-artemether group, 25,500/ $\mu$ L for the lumefantrine tablet group, and 23,800/ $\mu$ L for the lumefantrine capsule group. In this clinical trial, the 28 day parasitological cure rate in the ITT population was 96.2% (50/52) in the CGP56697 group, 88.2% (45/51) in the lumefantrine tablet group and 94.0% (47/50) in the lumefantrine capsule group. PCT for co-artemether (30 hours) was statistically significantly faster than with either lumefantrine tablets (48 hours) or capsules (54 hours). The sponsor concludes that while lumefantrine monotherapy was effective in terms of 28-day parasitological cure rates, it was slower than co-artemether in clearing parasites, and that the combination of artemether with lumefantrine is more effective than either component used as monotherapy. No serious adverse events were reported. No drug related signs or symptoms were found. Hematological and blood chemistry parameters were felt to be typical of those seen with malaria patients.

**Protocol ABMO2:** A randomized, parallel group, comparative *Plasmodium falciparum* trial of an oral anti-malarial drug combination, co-artemether, and one of its components, benflumetol (2 formulations), given to patients with infection: a combined pharmacokinetic and efficacy trial in China

The efficacy of the combination as compared with its individual components was further investigated in this randomized, parallel group trial. This study enrolled patients aged 13 to 60, male or female, with symptomatic previously untreated *P. falciparum* infection. Patients with signs of severe or complicated falciparum infection or treatment with anti-malarial drugs during the preceding 4 weeks before the start of the trial were excluded. This single investigator, single site trial was conducted between June, 1994 and October, 1994. A 4-dose regimen of co-artemether (80 mg artemether plus 480 mg lumefantrine) was compared with the same regimen of each individual component in adult patients with uncomplicated *P. falciparum* malaria. During the first 96 hours, patients were monitored for parasites (blood microscopy) at 6 hourly intervals until parasites were cleared for 12 hours and then once daily until Day 29. During the first 96 hours, temperature was monitored at 6 hourly intervals until the subject was afebrile for 12 hours and then twice daily until Day 29. A 12-lead ECG was performed on Days 2, 3, 4, 6, and 7. Hematology (full blood count including differential white blood cell count, platelet count, and reticulocyte count), biochemistry (bilirubin, alkaline phosphatase, SGOT, SGPT, sodium, potassium, glucose, creatinine, and urea), and urinalysis (albumin, glucose, bilirubin, and blood) studies were performed on Days 4, 8, 15, 22, and 29. Follow-up ended at Day 29.

The primary efficacy variables were defined as

- 28 day cure rate defined as the proportion of patients with clearance of asexual parasitemia within 7 days of initiation of trial treatment, without subsequent recrudescence
- PCT
- FCT

The secondary efficacy variable was defined as anti-gametocyte activity. Also analyzed was the parasite reduction at 24 hours after initiation of trial treatment, although this was not prespecified in the protocol.

### Brief Summary of Results

Asexual parasitemia ranged from 1,038 to 162,771/  $\mu$ L. The combination of artemether and lumefantrine demonstrated a 94.3% (50/53) 28-day parasitological cure rate, while artemether alone demonstrated a 46.2% (24/52) cure rate and lumefantrine alone demonstrated a 90.4% (47/52) cure rate in the ITT population. The combination was also associated with a more rapid clearance of parasites (30 hours) and fever (30 hours) than lumefantrine (54 and 60 hours, respectively). One patient treated with lumefantrine alone had diarrhea on Days 3 to 5 and bloody stool on Days 4 and 5. No further adverse experiences were recorded during the trial. In all three treatment groups, lengthening of the QTc interval in the range of 5-10% was noted. Hematological and blood chemistry parameters were felt to be typical of those seen with malaria patients.

**Protocol A025:** A randomized, double-blind, parallel group trial confirming efficacy, safety and pharmacokinetics of the standard schedule (4x4 tablets over 48 hours) with two higher dose schedules of co-artemether in the treatment of acute *Plasmodium falciparum* malaria in adults and children in Thailand

This Phase 2 trial was conducted at 2 sites in Thailand between September, 1996 and March, 1997; a third site in Thailand was planned but never initiated. The trial was a randomized, double-blind, parallel group trial comparing the standard schedule at the time of the study of co-artemether (4 doses over 48 hours) with two higher doses (6 doses over 60 hours and 6 doses over 96 hours). Male and female adults and children, age greater than 2 years, with confirmed acute, uncomplicated *P. falciparum* malaria (with asexual parasitemia above 500/ $\mu$ L) were included in the study.

Hospital inpatients at Site 1 (Dr. Looareesuwan) were monitored at 12 hourly intervals by blood microscopy until parasite clearance and by oral temperature for the first 72 hours. Afterwards temperature was measured and blood microscopy performed once daily until Day 8. Thereafter, the patient was seen daily between Days 8 and 29; blood microscopy and temperatures were checked weekly. At site 3 (Dr. Nosten), the subjects were treated as outpatients. Patients were monitored daily during the first week by blood microscopy until parasite clearance and by oral temperature. Thereafter, the patients visited the clinic weekly and temperature measurements were taken and blood microscopy performed. Blood samples for PCR were taken at baseline and at the day of reappearance of parasites. ECGs were performed at Site 1 only, at baseline and Days 3, 4, 5, 8, and 29. At Site 1, hematology (full blood count including differential white blood cell count, platelet count, and reticulocyte count), blood chemistry (bilirubin, alkaline phosphatase, SGOT, SGPT, sodium, potassium,

glucose, creatinine, urea, total protein, and albumin), and urinalysis studies were performed on Days 1, 4, 6, 8, and 29. Follow-up ended at Day 29; at site 3, a follow-up visit occurred at Day 64. At site 3, only standard hematology (hemoglobin, hematocrit, WBC, neutrophils, lymphocytes, and platelets) was performed on Days 1, 4, 8, and 29.

The primary efficacy variable is given as the 28 day cure rate in the protocol, defined as the proportion of patients with clearance of asexual parasitemia within 7 days of initiation of trial treatment, without subsequent recrudescence. Secondary efficacy variables are PCT, parasite reduction at 24 hours, and FCT.

### Brief Summary of Results

The majority of the patients in the study were males (70%) with an age range of 3 to 75 years (median 23 years); 43 of the 359 subjects total enrolled in the study were children  $\leq$  12 years old. Parasitemia ranged from 290 to 464,880/ $\mu$ L. The 28 day cure rates were higher in the ITT population for both 6 dose regimens: 81.4% (96/118) for the 60 hours group, 86.0% (104/121) for the 96 hour group, and 70.8% (85/120) in the 4 dose group. Efficacy was similar in the

Per Protocol population. No difference in the PCT, parasite reduction at 24 hours, and FCT was seen between the treatment groups. Five serious adverse events (SAEs) were reported, including 2 fatalities (one patient was shot and one was killed in a mine); no SAE was deemed related to study drug. In all treatment groups, headache was the most frequent AE recorded after baseline. A few digestive system symptoms were recorded more frequently in the 96 hour regimen (abdominal pain, nausea, and vomiting). Dizziness was reported less frequently in the 96 hour group than in either of the two shorter regimens. In 5 subjects, the QTc interval increased by more than 60 msec over baseline, but only in two of these subjects did it also exceed normal values. Hematological and blood chemistry parameters were felt to be typical of those seen with malaria patients, and improvement was noted with anti-malarial treatment.

**Protocol A026:** A randomized trial confirming efficacy and safety of the high dose regimen of CGP 56697 (in comparison with mefloquine + artesunate) in the treatment of acute *Plasmodium falciparum* malaria in adults and children in Thailand

This Phase 3B trial was conducted at 2 sites in Thailand (the same 2 sites and investigators as Study 025) between November, 1997 and March, 1998. The trial was a randomized (3:1), open-label, comparative, parallel group trial which enrolled male and female adults and children, aged 2 years of more, with confirmed acute, uncomplicated *P. falciparum* malaria (with asexual parasitemia above 500/ $\mu$ L). Patients with signs of severe or complicated *P. falciparum* were excluded. CGP56697 was given as the 6 dose regimen (6x4 tablets at 0 and 8 hours and twice daily thereafter; the number of tablets for each dose was adjusted according to body weight. Artesunate was administered in a 4 mg/kg dose once daily for 3 days, together with mefloquine 25 mg/kg given as a split dose of 15 mg/kg plus 10 mg/kg on Days 2 and 3.

Patients were seen daily from Days 1 through 8, and subsequently on Days 15, 22, and 29. Blood microscopy for parasites was performed daily on Days 1 through 4, with a continuation through Day 7 if parasites had not yet cleared. Blood microscopy for parasites was then performed on Days 8, 15, 22, and 29. Oral temperature was monitored on the same schedule.

ECGs were performed at baseline and prior to dose 2 (or 3), within 4 hours of dose 4 (or prior to dose 5), within 4 hours of dose 6, 8-16 hours after dose 6, and Day 29. At Site 1 (Dr. Looareesuwan), hematology (hemoglobin, hematocrit, RBC, WBC total, differential count, platelets, and reticulocytes), chemistry (total bilirubin, alkaline phosphatase, SGOT (AST), SGPT (ALT), sodium, potassium, glucose, creatinine, urea, total protein, and albumin), and urinalysis (albumin, glucose, bilirubin, and blood via dipstick) were obtained on Days 1, 4, 8, and 29. At Site 2 (Dr. Nosten), only selected hematology studies (hematocrit, WBC, neutrophils, lymphocytes, and platelets) were obtained on the same days. The last day of follow-up was Day 29.

The primary efficacy variable is given in the protocol as the 28 day cure rate, defined as the proportion of patients with clearance of asexual parasitemia within 7 days of initiation of trial treatment, without subsequent recrudescence. Secondary efficacy variables are parasite reduction at 24, 48, and 72 hours after initiation of trial treatment, proportion of patients with a negative slide on Days 2, 3, and 4, and anti-gametocyte activity (clearance of gametocytes existing at baseline at Days 2, 3, 4, 8, 15, 22, and 29).

#### Brief Summary of Results

There were 150 subjects enrolled in the CGP 56697 arm and 50 subjects enrolled in the mefloquine/artesunate arm. The majority of the subjects were males (74%), with an age range of 2 to 63 years (median of 22 years); 34 (17%) of the subjects were children  $\leq$  12 years of age. Parasitemia ranged from 264-254,490/ $\mu$ L. The 28 day cure rate in the CGP 56697 arm in the ITT population was 86.7% (130/150) and in the mefloquine/artesunate arm was 94.0% (47/50); the results in the Per Protocol population were 97.0% (130/134) and 100% (47/47), respectively. Both treatments cleared parasites rapidly. After about 24 hours more than 99% of the baseline parasitemia was eliminated and about 90% of the subjects had cleared their parasitemia within 48 hours. Both treatments also cleared gametocyte forms rapidly. Two SAEs were reported: generalized pruritic urticaria (mefloquine/artesunate arm) and febrile coma of unknown origin (CGP 56697 arm). Symptoms such as sleep disorder, arthralgia, myalgia, abdominal pain, anorexia, palpitation, dizziness, headache, and asthenia appear to have been caused or worsened by CGP 56697 in more than 10% of subjects in this trial, and in a higher percentage of mefloquine/artesunate treated subjects. A similar percentage of subjects in each treatment group experienced QTc prolongation. Hematological and blood chemistry parameters were felt to be typical of those seen with malaria patients, and improvement was noted with anti-malarial treatment.

**Protocol A028:** A randomized open-label trial (in comparison with MAS) confirming efficacy and safety of the 6-dose regimen of CGP 56697 using FMI in the treatment of acute *Plasmodium falciparum* malaria in patients aged > 12 years in Thailand

This Phase 3b trial was conducted at a single site in Thailand between September, 1998 and January, 1999; the same investigator participated in Studies A025 and A026. The trial was a randomized (3:1), open-label trial comparing the safety and efficacy of the 6 dose regimen of CGP 56697 (6x4 tablets at 0 and 8 hours and twice daily thereafter) with mefloquine (25 mg/kg given as a split dose of 15 mg/kg plus 10 mg/kg on Days 2 and 3) and artesunate (4 mg/kg once daily for 3 days). This study enrolled male and female patients, >12 years and >35

kg, with confirmed acute, uncomplicated *P. falciparum* malaria. Patients with known hypersensitivity to artemisinin or mefloquine derivatives, or signs of severe or complicated *P. falciparum* were excluded. Patients were monitored thrice daily for the first 3 days (or until clearance was reached) by blood microscopy and by temperature. Patients were to attend the one-week follow-up (Day 8) for evaluations of temperature, blood microscopy, ECG, vital signs, lab tests, and any adverse events or concomitant medications were to be recorded. Patients were to be followed for 4 weeks with weekly visits ( $\pm 2$  days). PCR was used to distinguish between recrudescence and new infection. A 12-lead ECG was performed on Days 1, 2, 3, 4, 8, and 29. Hematology (hemoglobin, hematocrit, RBC, WBC total with differential count, and platelets), chemistry (sodium, potassium, glucose, creatinine, urea, total protein, and albumin), and urinalyses (albumin, glucose, bilirubin, and blood) were performed on Days 1, 4, 8, and 29. Follow-up ended at Day 29.

The protocol specifies that the 6-dose regimen would be considered effective if the lower limit of the 90% CI for the 28 day cure rate exceeds 85%. Further efficacy measures were: parasite reduction at 24 hours after initiation of trial treatment, PCT, FCT, and anti-gametocyte activity.

#### Brief Summary of Results

The majority of the patients in the study were males (71%), with an age range of 12 to 71 years (median age 25 years). Parasitemia ranged from 13 to 436,050/ $\mu$ L. In the CGP 56697 group 10% of subjects discontinued the study prematurely, as did 4% of the mefloquine/artesunate group; the most common reason was loss to follow-up. The 28-day cure rates were 90.2% (148/164) in the CGP56697 group and 96.4% (53/55) in the mefloquine/artesunate group in the ITT population; similar results were seen in the Per Protocol population. Both treatments cleared parasites rapidly (100% at 24 hours). One serious adverse event was reported in the CGP 56697 group: dyspnea and pulmonary edema due to fluid overload deemed unrelated to study drug treatment. The majority of adverse events reported were symptoms typical of malaria although classified as treatment emergent (abdominal pain, dyspepsia, nausea, vomiting, diarrhea, anorexia, and constipation in 18.3% of the CGP 56697 group and 21.8% of the mefloquine/artesunate group. Nervous system symptoms (headache, dizziness, sleep disorder) were reported in 27.4% of subjects in the CGP 56697 group and 16.4% in the mefloquine/artesunate group). No clinically relevant increases in the QTc interval were seen. Hematology and blood chemistry parameters were felt to be typical of those seen with malaria patients, and improvement was noted with anti-malarial treatment. In three subjects a clinical adverse event of jaundice was noted after treatment with CGP 55697. In all of these cases, the bilirubin was elevated at baseline and resolution occurred on follow-up.

**Protocol A2403:** Open label, multi-center study for the evaluation of safety and efficacy of Coartem<sup>®</sup> (artemether-lumefantrine) tablets (6-dose regimen) in African infants and children in the treatment of acute uncomplicated falciparum malaria

This Phase 3 study was conducted at three sites in Africa (Kenya, Nigeria, and Tanzania) between July, 2002 and February, 2003. The trial was an open label, noncomparative study using the 6-dose Coartem<sup>®</sup> regimen in infants and children weighing  $\geq 5$  kg to  $\leq 25$  kg. Tablets were dispensed in blisters containing 8 tablets (six for treatment according to body weight and two replacement tablets in case of vomiting). Male and premenarchal females

weighing  $\geq 5$  kg to  $\leq 25$  kg with microscopically confirmed acute uncomplicated *P. falciparum* malaria were enrolled. Exclusion criteria were “danger signs of severe malaria” or severe malaria, other plasmodium infections, receipt of any drug known to influence cardiac function prior to Screening or other continuing malaria treatment, serious gastrointestinal disease, severe malnutrition or severe anemia, or consumption of any drug metabolized by cytochrome enzyme CYP2D6. Full physical examinations, including a full neurological exam, were carried out at baseline and at Days 3, 7, 14, and Day 28 or at the time of withdrawal. Safety monitoring consisted of hematology (hematocrit, hemoglobin, RBC, WBC with differential, and platelet count), biochemistry (glucose, bilirubin, creatinine, ALT (SGPT), ASP (SGOT), serum gamma-glutamyl transferase, and G6PD (at baseline only)), urinalyses if deemed necessary by the investigator (hemoglobin, protein, and sediment), stool sample if deemed necessary by the investigator (swab for ova and parasites); laboratory safety monitoring was conducted at screening and on Day 3, 7, and 28. Malarial blood smears were obtained at screening, at 8 hours and then twice daily on Days 2 and 3, with subsequent blood smears obtained on Days 7, 14, and 28. A blood sample for identification of infectious agents was obtained at the start of the study. Alkaline phosphatase was collected with other safety laboratories at Center 2 and 3 and amylase was collected at Center 3. Patients were on the study for a total of 28 days. ECGs were recorded at baseline and Day 3.

The primary objective of this study was to assess the safety of the 6-dose regimen in African infants and children. The following efficacy variables were summarized descriptively:

- Development of danger signs or severe malaria on Days 1, 2, and 3
- FCT
- PCT
- Time to gametocyte clearance
- 7 day cure rate
- 14 day cure rate
- 28 day cure rate

The efficacy analyses were to be performed primarily on the Per Protocol population with supportive analysis on the ITT population.

#### Brief Summary of Results

A total of 310 subjects were enrolled and analyzed. Of these, 154 subjects were in the 5-<10 kg weight group, 110 were in the 10-<15 kg weight group and 46 were in the 15- $\leq$ 25 kg weight group. Baseline parasitemia ranged from 1,000 to 138,000/ $\mu$ L. Most subjects received the full 6-dose regimen of Coartem<sup>®</sup>. Cure rates at 28 days for the ITT population were 86.4% (133/154) in the 5-<10 kg group, 85.5% (94/110) in the 10-<15 kg group, and 89.1% (41/46) in the 15- $\leq$ 25 kg group. In the PCR corrected analysis, the 28 day cure rates were 94.2% (145/154), 93.6% (103/110), and 93.5% (43/46), respectively. Cough, anemia, vomiting, anorexia, and diarrhea were the only adverse events reported in more than 10% of patients. Most adverse events were mild, and the adverse events observed were not unexpected in this patient population. There were four serious adverse events: gastroenteritis which occurred after the end of treatment, with death as a result; viral hepatitis; malaria/convulsions; and severe urticaria (the only SAE thought to be treatment related). Laboratory evaluations revealed no unexpected effects on hematology, biochemistry, or urinalysis parameters.

According to Bazett's correction, 4% of infants had QTc prolongation; most cases were in the 5-<10 kg body weight group.

**Protocol B2303:** A randomized, investigator-blinded, multicenter, parallel-group study to compare efficacy, safety and tolerability of Coartem<sup>®</sup> dispersible tablet vs. Coartem<sup>®</sup> 6-dose crushed tablet in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in infants and children.

This multicenter Phase 3B trial was conducted at 8 sites in Africa (Benin, Kenya, Mali, Mozambique, and Tanzania) between August, 2006 and March, 2007. It was a randomized (1:1), investigator-blinded, parallel-group trial using the Coartem<sup>®</sup> dispersible tablet (dose based on body weight range) using the Coartem<sup>®</sup> standard (crushed) tablet as a control. The study enrolled males and female infants and children  $\leq 12$  years of age with a body weight of  $\geq 5$  kg and  $< 35$  kg, with microscopic confirmation of acute uncomplicated *P. falciparum* malaria or mixed infection including *P. falciparum* using Giemsa-stained thick film *P. falciparum* parasitemia of  $\geq 2000$  and  $< 200,000$  parasites/ $\mu$ L and fever  $\geq 37.5^{\circ}\text{C}$  (axillary temperature) or  $\geq 38^{\circ}\text{C}$  (rectal temperature), or history of fever in the preceding 24 hours. Subjects excluded include those with signs/symptoms indicative of severe/complicated malaria, Plasmodium infection without *P. falciparum*, other antimalarial received within 14 days of trial start, serious gastrointestinal disease, severe malnutrition or kwashiorkor, severe anemia, known disturbances of electrolyte balance, inability to drink or being breastfed, a history of hypersensitivity to any of the study drugs or to drugs with similar chemical structures, history or family history of long QT syndrome or sudden death or other conditions known to prolong the QTc interval, presence of QTc interval prolongation, or known chronic underlying disease. Also excluded were subjects taking cotrimoxazoles and those who received any anti-malarial drug known to influence cardiac function within 4 weeks prior to the screening visit and those taking drugs that are known to influence cardiac function and prolong the QTc interval. Malaria blood smears were performed twice daily before dosing of Coartem<sup>®</sup> and during Days 2 and 3; smears were performed daily on Days 4, 7, 14, 28, and 42, at the time of withdrawal, and when malaria was suspected. Body temperature was monitored on the same schedule. Hematology and biochemical monitoring were performed on Days 0/1, 3, 7, 28, and 42. PCR genotyping was conducted on samples from Day 0/1 and at the time of reappearance of parasites. ECGs were done on subjects prior to the first dose of the study medication and 6-10 hours after the last dose. Follow-up ended at Day 42.

The primary objective of the study was to demonstrate the non-inferiority of the 6-dose regimen of the dispersible tablet to the 6-dose regimen of crushed tablet with respect to the 28-day PCR-corrected parasitological cure rate. The primary efficacy endpoint was the PCR-corrected parasitological cure rate at 28 days in the ITT population who completed 38 days with a valid PCR evaluation (PA population) or were treatment failures prior to the Day 28 visit. Secondary efficacy variables included 7-day parasitological cure rate, PCR-corrected 14-day parasitological cure rate, PCT, FCT, and time to gametocyte clearance.

#### Brief Summary of Results

A total of 899 infants and children were enrolled in the trial; the median age was 3 years and the median body weight 13 kg. Over half of the patients were in the age range 2-<6 years. The

median parasite density was slightly lower in the dispersible tablet group (26,364/ $\mu$ L) than in the crushed tablet group (32,288/ $\mu$ L). The PCR- corrected 28-day cure rate in the PA population was 97.8% (394/403) for the dispersible tablet and 98.5% (403/409) for the crushed tablet. Similar results were noted in the ITT and Per Protocol populations. The most frequent adverse events were pyrexia, cough, *P. falciparum* infection, and vomiting. The majority of adverse events were mild or moderate in severity. The incidence of cardiac adverse events was low and none were reported as serious adverse events. There were 3 deaths during the study: in the dispersible tablet group, one subject died from a hemorrhage and one from an infection. In the crushed tablet group, one subject died from severe *P. falciparum* infection. No death was suspected to be related to the study drug. No serious adverse event was suspected to be related to the study drug; most were infections. No patient had a QTc interval of >500 msec, and a low rate of QTc interval increases of >60 seconds were observed. Laboratory evaluations showed hematology and biochemistry profiles generally consistent with the course of malaria and its resolution after treatment.

## II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Interim Classification	Final Classification
Jiao Xiu-Qing, M.D. (retired) Contact at site = Dr. Jingyan Wang Institute of Microbiology and Epidemiology, The Academy of Military Medical Sciences, No. 20 Fengtai East Street, Beijing 100071, China Tel.: +86 10 66948546, or +86 13611183711 FAX: +86 10 63813346 E-mail: wangjy@nic.bmi.ac.cn	Protocol A023: 153	Pending	Pending	Pending
Jiao Xiu-Qing, M.D. (retired) Contact at site = Dr. Jingyan Wang Institute of Microbiology and Epidemiology, The Academy of Military Medical Sciences, No. 20 Fengtai East Street, Beijing 100071, China Tel.: +86 10 66948546, or +86 13611183711 FAX: +86 10 63813346 E-mail: wangjy@nic.bmi.ac.cn	Protocol ABOM2: 157	Pending	Pending	Pending

Dr. Sornchai Looareesuwan* (Deceased) Faculty of Tropical Medicine, Mahidol University 420/6 Rajavithree Road, Rajathewee, Bangkok 10400, Thailand Tel.: +66 2 354 9159 FAX: +66 2 354 9158 E-mail: <a href="mailto:tmsks@mahidol.ac.th">tmsks@mahidol.ac.th</a>	Protocol A025: 100 Protocol A026: 28 Protocol A028: 219	10/20-10/24/08, 10/27- 10/28/08	VAI	Pending
Prof. Francois Nosten Shoklo Malaria Research Unit 68/30 Baan Tung Road, PO Box 46 Mae Sot Tak 63110 Thailand Tel.: +66 55 545 021 Mob. Tel.: +668 1881 3350 FAX: +66 55 5545 020 E-mail: <a href="mailto:francois@tropmedres.ac">francois@tropmedres.ac</a>	Protocol A025: 259 Protocol A026: 172	10/13-10/31/08	Pending	Pending
Dr. Michael Makanga Kenya Medical Research Institute KEMRI Kilifi, Kenya Current contact info: Francie van Zijl Drive, Parow PO Box 19070, Tygerberg 7505 Cape Town, South Africa Tel.: +27 21 938 0509 FAX: +27 219380569 E-mail: <a href="mailto:Makanga@edctp.org">Makanga@edctp.org</a>	Protocol B2403: 107	10/13-10/17/08	VAI	Pending
Prof. Zul Premji Muhimbili University United Nations Road Box 65011 Dar es salaam, Tanzania Tel.: +255 754304468 FAX: +255 22 2150465	Protocol B2403: 100	10/20-10/24/08	VAI	Pending
Dr. Salim Abdulla Ifakara Health Research and Development Centre Dar es salaam, Tanzania Current contact info: Bagamoyo Research and Trainig Unit Ifakara Health Research and Development Centre, Bagamoyo Branch, PO Box 74 Bagamoyo, Tanzania Tel.: +255 23 244 0064 Mob. Tel.: +255754744555 FAX: none E-mail: <a href="mailto:sabdulla@ihi.or.tz">sabdulla@ihi.or.tz</a>	Protocol A2303: 240	10/27/08 - ongoing	Pending	Pending
Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel – Switzerland	Protocol A023 Protocol ABOM2 Protocol A025			

Contact: Matthew Stoudemayer (Novartis East Hanover, New Jersey) Phone: (862) 778-0291 Fax: (973) 781-3132	Protocol A026 Protocol A028 Protocol B2403 Protocol A2303			
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\*The records for this site have been moved to a (b) (4)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

Coartem<sup>®</sup> is a new molecular entity for the treatment of malaria. The review team has no major concerns regarding the efficacy or safety of the drug based on the review to date of the data provided in the current NDA, and does not believe that any one site is driving efficacy results.

Studies 023 and ABOM2 were both performed by a single investigator in China. These two studies compare the safety and efficacy of Coartem<sup>®</sup> to that of its individual components, artemether and benflumetol (subsequently known as lumefantrine). However, the Coartem<sup>®</sup> regimen used in these two studies (4 doses of 4 tablets) differs from that intended for registration (6 doses of 4 tablets).

Comparative studies of Coartem<sup>®</sup> at the proposed labeling dose include Studies A025 (4 dose vs. 2 different 6-dose regimens), A026 (6-dose vs. mefloquine/artesunate), and A028 (6-dose vs. mefloquine/artesunate). Dr. Looareesuwan (Thailand) enrolled subjects in all three of these studies, and was the sole investigator in Study 028; the review team has requested that this site be inspected. Novartis has notified the review division that these records are available at a CRO in Bangkok near to the original site. In addition, a second investigator (Dr. Nosten, Thailand) enrolled the majority of subjects in Studies A025 and A026. The sponsor has stated that “limited” records are available at this site (listed as Investigator’s Patient Register; Ethics Committee approval; CRF & CRF filing manual; Normal Value for Laboratory; Lab books; Correspondence except consent forms). In order to establish the integrity of the data from the majority of the subjects enrolled in Studies A025 and A026, Dr. Nosten’s site in Thailand will be inspected; this data will ultimately support the use of the proposed labeled dose and duration of Coartem<sup>®</sup>. In addition, the review division notes that Studies A025 and A026 were conducted in an area of chloroquine-resistant *P. falciparum*.

The requested indication for Coartem<sup>®</sup> includes the treatment of uncomplicated *P. falciparum* malaria in infants and children  $\geq 5$  kg. There were relatively large numbers of infants and small children ( $\geq 5$ kg weight and upward) enrolled in Studies B2403 and A2303 conducted at several sites in Africa. The results of these studies contribute important safety and efficacy data regarding the use of Coartem<sup>®</sup> at the proposed labeling dose in infants and children, and the review division has requested that one or more of these sites be included for inspection.

There is no evidence at the current stage of review that any of the data submitted to the NDA is fraudulent or inconsistent. The studies included in the NDA were not conducted under IND. All studies listed above were conducted at non-U.S. sites.

1. **Dr. Sornchai Looareesuwan\***

**Faculty of Tropical Medicine**

**Mahidol University**

**420/6 Rajavithree Road**

**Bangkok, 10400 Thailand**

**\*Contact information: Dr. Srivicha Krudsood, Clinical Investigator at the same address/site; Dr. Looareesuwan is deceased.**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. The inspectors report that the total number of subjects screened at the site cannot be determined since screening was performed as part of the hospital admission process, with the study staff only confirming that a subject was appropriate for the study. For Study 025, 114 subjects were enrolled; for Study 026, 12 subjects were enrolled; and for Study 028, 79 subjects were enrolled. The records of 17 subjects were reviewed by the inspectors for Study 025, 12 records for Study 026, and 79 records for Study 028. <sup>(b) (4)</sup> The observations noted are based on preliminary communications with the FDA field investigators and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60 and did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b).

Protocol Violations [21 CFR 312.60]

1. Subjects were enrolled in both Studies 028 and 026 despite meeting the Exclusion Criterion of having a SGPT (ALT) of  $>2.5x$  the upper limit of normal. Specifically, 11 of the 79 subjects reviewed by the inspectors had a screening ALT ranging from 3.2 to 8.2 times the upper limit of normal (40 U/L). In Study 028, 1 of 12 subjects reviewed had a ALT of 8.3 times the upper limit of normal.
2. The protocol for Study 026 specifies that patients would be monitored daily during the first week by blood microscopy until parasite clearance and by oral temperature. Thereafter, the patients were to be visit the clinic weekly for temperature measurements and blood microscopy. Of the 12 subjects reviewed by the inspectors, 10 completed the trial, and only 3 were scheduled for all study visits. All were present for the Day 29 final visit. Of the 9 patients missing visits, 4 missed the weekly visits between Days 9-

28, 2 missed the weekly visits between Days 12-28, and 1 missed the weekly visit between Days 16-28.

Recordkeeping Violations [21 CFR 312.62(b)]

1. It is unclear whether reporting of SAEs from this site met the protocol requirements, which specify that SAEs are to be reported to the sponsor within 24 hours of “learning of its occurrence”. All SAEs from this site have an onset date more than 24 hours before the report of the SAE.
- c. **Assessment of data integrity:** Although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies. The data appear acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum*.

2. **Dr. Francis Nosten**  
**Shoklo Malaria Research Unit**  
**68/30 Baan Tung Road, PO Box 46**  
**Mae Sot Tak, 63110 Thailand**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. The inspectors report that the investigators did a prescreen and then entered subjects if qualified. There is no record of anyone failing screening. For Study 025, 259 subjects were screened and enrolled; for Study 026, 172 subjects were screened and enrolled. For Study 025, 206 subjects completed the study and 147 subjects completed Study 026. The records of 87 subjects were reviewed by the inspectors for Study 025 and 60 records were reviewed for Study 026. <sup>(b) (4)</sup>  
The observations noted are based on preliminary communications with the FDA field investigators and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60 and did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b).

Protocol Violations [21 CFR 312.60]

- i. In Study 025, Subject 439 experienced an increase in severity of malaria symptoms and was admitted to the hospital. This was

not recorded as an adverse event. The hospital record notes that the subject had “. . . convulsions in clinic II about 7:30...” The convulsion was not reported as a severe adverse event.

- ii. In Study 025, subject dosing did not always occur according to the schedule in the protocol in all 87 of the 259 subjects reviewed by the inspectors. All subjects reviewed received the 24 hour dose and following doses too early. For example, Subject 218 received dose 1 at 1400 and received the third “24 hour” dose at 0840 the next day.

*Medical Officer’s Comment: Given that the timing of the first 3 doses should be 0 hours, 8 hours, and 24 hours, it is unlikely that giving the 24 hour dose the next morning would result in significantly altered pharmacokinetics and/or efficacy. As long as most subjects did not receive their first dose relatively late in the day, the dosing interval should not be compressed enough to adversely effect the study.*

- iii. In Study 026, the timing of the blood microscopy for parasites was not as specified in the protocol. The protocol specified that “in all centres, baseline blood microscopy needs to be as close as possible to first dosing (i.e., repeat if more than 2 hours) and the 24 hours slide as accurately as possible 24 hours after start of treatment.” Of the 172 subjects enrolled at this site, only 22 had this test performed within 2 hours of the scheduled time 24 hours after the first dose.

*Medical Officer’s Comment: Although of significance in terms of proper study conduct, this finding is unlikely to affect the primary efficacy outcome of clearance of parasitemia within 7 days of initiation of trial treatment.*

Recordkeeping Violations [21 CFR 312.62(b)]

2. In Study 026, the documentation of inclusion and exclusion criteria was either not in the patient chart or was incomplete for 8 of the 60 subjects reviewed.

- c. **Assessment of data integrity:** Although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies. The data appear acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum*.

3. **Dr. Michael Makanga**  
**Kenya Medical Research Institute**  
**KEMRI**  
**Kilifi, Kenya**  
**Current contact information: Francie van Zijl Drive, Parow, PO Box 19070,**  
**Tygerberg 7505, Cape Town, South Africa**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. For Study 2403, 456 subjects were screened and 107 subjects were enrolled, and 104 subjects completed the study; 3 subjects discontinued the study prior to conclusion. The records of 28 subjects were reviewed by the inspector, including subjects in all three study groups. The informed consent document was reviewed for all 107 subjects. (b) (4)
- The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.
- b. **General observations/commentary:** Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspector considered that there was no evidence of fraud and that Dr. Makenga appeared to be a dedicated and knowledgeable researcher.

However, the inspection documented that Dr. Makenga did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b).

Recordkeeping Violations [21 CFR 312.62(b)]

1. The source documents for the administration of test article to study subjects (Dosage Administration Records) do not include the name of the drug administered. In addition, the dosage administration records do not document who prepared and administered the drug to the study subjects.
2. When the dosage administration records did include the initials of the individual who prepared and administered the drug to study subjects, often the initials did not correspond to authorized study personnel identified in the "Clinical Trial Authorized Signature Log.
3. Study records do not identify who dispensed the test article from the on-site pharmacy to study personnel. In addition, pharmacy staff that were responsible for dispensing test article to study staff are not identified in the clinical trial authorized signature log.
4. There is no documentation in the study records to indicate that the investigator had the written approval/favorable opinion of the AIRB for the informed consent (IC) documents prior to the study. An English version of the written IC was reportedly submitted to the IRB with the study protocol. However, the IRB approval records do not specify that the IC documents were reviewed and approved. In addition, the English versions of the IC documents, reportedly submitted to the IRB with the protocol, were not used during the study. The versions used had reportedly been translated by study

staff into Swahili (official language of Kenya) and Giriana, a local dialect. Study records did not contain any certifications that the translated versions were compared against the English versions and found to be accurate, and the translated versions had not been submitted to the IRB.

5. Source data was not retained, in that blood slides, including those used to obtain parasitology and gametocyte counts, could not be located. Of a total of 40 slides requested for review by the inspector, only 16 could be located.
  6. For at least 43 of the 107 study subjects, the two written IC documents required for each study subject (general IC and PK sampling IC) were provided to study subjects' parent or guardian in different languages. For example, group 001 subjects 47, 48, 49, 51, 52, 53, and 54, group 002 subjects 1, 4, 15, 19, 21, 22, 23, 24, and 25-38 received their general IC documents in the Giriana dialect and their PK sampling consent forms in the Swahili language, with no explanation documented in study records for the discrepancy.
  7. Study records do not document that Serious Adverse Event (SAE) reports were faxed to the local Novartis Clinical Safety & Epidemiology Dept. or to the corresponding department in the U.K. within 24 hours of receipt, as required by the protocol. This includes two SAEs for subject 002/22 of urticaria/rash and atypical pneumonia; SAE for study subject 001/49 of jaundice/hepatitis; and SAE for subject 001/45 of malaria and convulsions.
- c. **Assessment of data integrity:** Although recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum*.

4. **Professor Zulfigarall Premji**  
**Muhimbili University**  
**United Nations Road**  
**Box 65011**  
**Dar es salaam, Tanzania**

- a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. For Study 2403, 501 subjects were screened and 100 subjects were enrolled, and 100 subjects completed the study; 3 subjects discontinued the study prior to conclusion. All source data was reviewed by the inspector for 25 subjects, including compliance with inclusion/exclusion criteria, blood sampling, ECGs, case report forms, and dosing. Source data including primary and secondary efficacy factors (including time to fever clearance, time to parasite and gametocyte clearance) and informed consents were reviewed for all 100 study subjects. (b) (4)

The observations noted are

based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

- b. General observations/commentary:** Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that Dr. Premji did not adhere to the investigational plan, in violation of 21 CFR 312.60 and did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b).

Protocol Violations [21 CFR 312.60]

1. For all 100 study subjects, the investigator did not use the protocol-specified method for determining parasite density per microliter of blood. The calculation method for parasite density used at the study site assumed that all subjects had a WBC count of 8000, since hematology determinations were performed off site, and values were not available until the following day. Use of this calculation method results in different values for parasite density than does correction with the subject's actual WBC count. In five subjects, the investigator failed to use the protocol-specified method for determining gametocyte counts.

*Medical Officer's Comment: The primary efficacy outcome for this study is clearance of parasitemia, i.e. that time at which a subject no longer has detectable parasitemia. This reflects an all or none phenomenon – presence or absence. Therefore, the failure to use the protocol-specified method for calculation density is unlikely to affect the primary efficacy outcome and the outcome of the study. It may, however, result in skewing of the results of other calculated variables for the study. This issue was discussed with the review division's lead microbiologist, and she agreed that this finding is unlikely to affect data integrity.*

Recordkeeping Violations [21 CFR 312.62(b)]

1. The investigator did not maintain source data in study records.
  - i. The actual parasite and gametocyte counts obtained by blood microscopy at screening and at seven additional time points during the study were not documented in study records for any subject. The study records do contain calculated values for the parasite density per microliter (all subjects) and the gametocyte density per microliter (five subjects). The calculation of these parameters required the use of the blood microscopy results.
  - ii. The screening log which was utilized during the study to record patient screening information, including reasons for exclusion, could not be located. Present at the site was a typed summary printout, reportedly prepared from information contained in the missing screening log.
  - iii. In at least 65 of the 100 subjects, study records do not include blood hemoglobin values reportedly measured on-site during screening to ensure that the hemoglobin was > 5 g/dl. These on-site measurements were reportedly used to enter subjects into the study and initiate dosing without

waiting for the off-site hematology results, which would return the following day.

2. The study records for subject 002/10 do not document that his hemoglobin at study entry was  $\geq 5$  g/dl; hemoglobin of  $\leq 5$  g/dl is an exclusion criterion for this study. The hematology report for the study entry blood sample (9/4/02) (received by the site the following day) indicates that the test was not run as the blood sample was clotted. No hematology reports were included for this subject until 9/7/02.
  3. Subject 002/02<sup>(b) (4)</sup> was entered into the study with initiation of dosing on 8/28/02. However, the informed consent document was not signed until 8/30/02, by which time the subject had received 3 doses of study drug.
  4. For subject 001/08<sup>(b) (4)</sup> parasite density per microliter of blood at screening was incorrectly reported in the case report form and included in the sponsor's database, as 6400. However, the source data in the lab notebook shows the actual parasite density calculation to be 64,000.
  5. There is no documentation in the study records to indicate that the investigator had the approval of the IRB for the written informed consent document prior to the beginning of the study. The FDA inspector reports that an English version and a Swahili version of the written informed consent document were submitted to the IRB with the study protocol. However, the IRB approval records do not specify that the informed consent documents were reviewed and approved.
- c. **Assessment of data integrity:** Although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum*.
5. **Dr. Salim Abdulla**  
**Muhimbili University**  
**United Nations Road**  
**Box 65011**  
**Dar es salaam, Tanzania**
- a. **What was inspected:** The inspection at this site for Protocol 2303 is ongoing at the time of this review; five of the planned eight days have been completed. The CIS is being completed now so that the results can be incorporated into the briefing package for the Advisory Committee. The inspector reports that the screening log is incomplete, and that it fails to include 10 subjects who were enrolled; it was not possible to determine how many patients are not included that were screened and excluded. The site enrolled 242 subjects; two were screening failures, so 240 completed the study. Efficacy endpoint data was checked for approximately 190 of the

subjects. Also, 80 the informed consent documents of 80 subjects were checked, and the inspector plans to check 20 more. Full reviews of additional subjects are continuing at the time of this review. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigators. An inspection summary addendum will be generated after receipt and review of the final EIR. There were no limitations to the inspection.

- b. **General observations/commentary:** The primary efficacy endpoint is verifiable. The following preliminary issues have been identified so far:
1. The test article preparation and dispensing log is incomplete and suffered water damage. The inspector reports that a good portion of this source data has been manipulated and rewritten in the log, with an attempt made to pass it off as source data. In addition, the log is missing source data for the test article selection, preparation and dispensing to 12 of the 240 patients who completed the study.
  2. A study nurse was in the room when the drug was prepared, where she could see how the drug was prepared, with a mortar & pestle being used for standard Coartem versus a vial of water for the dispersible Coartem. The same nurse subsequently administered the test article to a number of subjects and was responsible for some patient care (e.g., vital signs). The protocol requires that the drug be dispensed and administered by an independent study person.
  3. There were three instances of parasite data discrepancies between source and the database, at the 8-hour time interval, but that derives from only three of “very many” checked.
- c. **Assessment of data integrity:** There appear to be protocol and record keeping violations at Dr. Abdulla’s site, on the basis of the information audited thus far after the first week of the inspection. Some of these deficiencies are still undergoing investigation. In particular, the attempts to repair the damaged preparation and dispensing log are of concern. We are waiting for further information to clarify the extent of this problem. At the present time, we cannot state definitively that the data are acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum*. Given that the inspection is still ongoing, and concerns about drug disposition have arisen, the review division may choose to consider an additional analysis excluding this site from the efficacy outcome. After completion of the inspection and receipt of the EIR, an inspection summary addendum will be generated after the results have been evaluated by DSI.

6. **Dr. Jiao Xiu-Qing, M.D.**  
**Institute of Microbiology and Epidemiology**  
**The Academy of Military Medical Sciences, No. 20**  
**Fengtai East Street, Beijing 100071, China**

a. **What was inspected:** This inspection is currently scheduled to start in mid-November.

7. **Sponsor/Monitor/CRO**

Novartis Pharma AG  
Lichtstrasse 35  
CH-4056 Basel – Switzerland  
Contact: Matthew Stoudemayer (Novartis East Hanover, New Jersey)

a. **What was inspected:** The FDA investigators reviewed Novartis procedures and records for protocols A023, ABKMO2, A025, A026, A028, A2401, A2303, and B2303. The inspection began on October 27, 2008 and is scheduled to conclude during the week of November 2, 2008. The inspector reviewed the Organization and Personnel, Site Selection, Monitoring Procedures and Activities, Record Retention, as well as Test Article Integrity and Accountability records of the eight pivotal studies submitted for this NDA (all of the studies inspected as well as A2401). Neither the EIR nor the Form FDA 483 (if generated) was available at the time this CIS was written; this CIS is being generated now to meet the deadline for the review division's Advisory Committee briefing package. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated after receipt and review of the final EIR. There were no limitations to the inspection.

b. **General observations/commentary:** The following preliminary observations were made by the inspector during the first week of two planned at Novartis:

1. There are unanswered questions regarding study medication in Study ABMO2. Immediately prior to initiation of the study, a fax was sent to the CRA requesting that study medication in short supply be replaced with new medications to be shipped to the CRA. Novartis stated that this never happened. However, it appears that the study medications were not packaged according to existing standard operating procedures (SOPs). The study medications were manufactured and packaged in China; however, the inspector reports that it is possible that additional API was shipped from Basel. The inspector is still working to clarify these issues. However, he does note that there are faxes and final instructions as to how the study medications were finally packaged and released for use missing between the CRA and the study director.

2. The protocol for Study ABMO2 specified laboratory monitoring to include glucose, BUN, creatinine, and total bilirubin. These tests were conducted on site and reported in mg/dl. These values were converted to micromoles/L and then transferred to the Case Report Form. There was no SOP for the conversion, no record of the original lab reports, nor any indication that the accuracy of the calculations was checked by the on-site monitor. The sponsor is checking to see if this issue occurred in any other study.
  3. The packaging records for the first one half of the study doses could not be located and are thought to be lost. This packaging record is where the firm identifies the batch or lot that was packaged for patient use for this clinical trial. Novartis is attempting to locate secondary documents to identify and verify which lot was used in the study.
  4. The following studies had monitoring issues:
    - i. Study B2303: the closeout Monitoring report was missing with several unresolved issues still being under review
    - ii. Study A025: the closeout Monitoring report was missing
    - iii. Study A026: the Initiation report at Site 02 was missing
    - iv. Study A2303: the Initiation report was missing
    - v. Study A2401: the Initiation report was unsigned
    - vi. Study A023: the Initiation and Closeout reports were missing
  5. Studies that were either blinded or had a blinded arm (A025, ABMO2, and A023) were provided a sealed envelope containing a “code break” to be used in the event of a serious adverse event. Code breaks for all three sites could not be located in the firm’s archived master trial folder. In addition, the SOP calls for the CRA to identify the code break envelopes, note if they are sealed or unsealed in the closeout Monitoring report, and return the envelopes to Novartis. This was not done for Studies A025 or ABMO2.
- c. **Assessment of data integrity:** The data collected and maintained at the sponsor’s site, as it pertains to the eight clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348.810 appear consistent with that submitted to the agency as part of and in support of NDA 22-192 after the first week of the inspection. As this inspection is still pending completion, DSI is unable to make an assessment on impact of preliminarily noted deficiencies on data integrity. However, DSI will notify the review division with any updates after this inspection is completed that would affect data integrity. After completion of the inspection and the EIR is received, an inspection summary addendum will be generated the results have been evaluated by DSI.

#### **IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

In general, the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. The inspections

documented minor regulatory violations at the sites of Drs. Looareesuwan, Nosten, Makenga, and Premji regarding protocol and recordkeeping violations. In general, the studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication. The inspections for Protocols A023 and ABOM2, both conducted solely by Jiao Xiu-Qing, M.D in China, have not yet taken place.

More preliminary information from the inspector in Tanzania indicates regulatory violations at the site of Dr. Abdulla. The description of attempts to alter/replicate the damaged test article and dispensing log are of concern, and at this time, the extent of this problem has not yet been defined. Therefore, DSI is unable to make an assessment of impact on data integrity. If drug dispensation to subjects can't be verified, the review division will need to consider excluding this data from the efficacy analysis. The preliminary report of the incomplete sponsor inspection of Novartis revealed some deficiencies that are still being examined as the inspection is ongoing. DSI will notify the review division as soon as possible if deficiencies are identified after completion of the inspection that would affect study outcome.

Follow-Up Actions: The observations noted above for Drs. Looareesuwan, Nosten, Makenga, and Premji are based on preliminary communications with the FDA field investigators and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. For the ongoing and pending inspections, an inspection summary addendum will be generated after the inspections have been completed and the results have been evaluated by DSI.

*{See appended electronic signature page}*

Susan D. Thompson, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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/s/

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Susan Thompson  
11/3/2008 04:28:22 PM  
MEDICAL OFFICER

Tejashri Purohit-Sheth  
11/3/2008 04:29:41 PM  
MEDICAL OFFICER



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**TRANSMITTAL SHEET**

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**DATE:** October 31, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via Email	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Clinical Information Request-Product Distribution Measures

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**Total no. of pages including cover:** 3

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**Comments: Concurrence**  
Joette Meyer, Pharm.D.

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**Document to be mailed:**  YES  NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our review team.

Please refer to your May 14, 2007 submission to pre-IND 75,287 which addressed the proposed trade name Coartem® for your product COA566, currently under Priority Review as NDA 22-268. After receipt and review of your May 14<sup>th</sup> submission, the Division of Special Pathogen and Transplant Products provided to you the findings from a Proprietary Name Risk Assessment via facsimile transmission (FAX) on April 28, 2008. On June 12, 2008 you submitted your responses to the April 28<sup>th</sup> comments to pre-IND 75,287.

In your June 12, 2008 submission you state, "...Coartem will not be stocked at retail pharmacies. It will be available only through 3 major wholesalers nationwide for distribution to a hospital or retail pharmacy request within 24 hours..."

- Please elaborate on the above statement, specifically is there a mechanism that would prevent a retail pharmacy from ordering and stocking Coartem® (for example, will a retail pharmacy be required to provide an actual prescription/medication order for a specific patient to the wholesaler before Coartem® would be shipped to them).
- If a mechanism like the one in the example above is utilized, then our understanding would be that the initiation of therapy could potentially be delayed for up to 24 hours, please comment.
- Based on only having 3 nationwide wholesalers, can it be concluded that Coartem® will be stocked in hospital pharmacies, please comment.

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo

10/31/2008 05:31:23 PM

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NDA 22-268 Facsimile Transmission Clinical Information Request Product Dist  
Measures



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**TRANSMITTAL SHEET**

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**DATE:** October 21, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via Email	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Additional comments to Applicant from October 15, 2008  
Division Presentation

**Total no. of pages including cover:** 4

**Comments:** Concurrence

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**Document to be mailed:**  YES  NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our review team. These requests address the parts of your Advisory Committee Briefing Book and Presentation Slides you presented to the Division on October 15, 2008.

#### Clinical Comments

1. Regarding your slide presentation, we noted that slides CC-40 and CC-41 show the results of the pooled efficacy analysis in adults and children, respectively, of the 4-dose regimen compared to the 6-dose regimen. We find that since the pooled analysis utilizes cross-study comparisons and is not based on comparative studies, the results presented in this manner are of limited value. We would find it more useful, if you presented a summary table of the results from each of the individual studies (one slide for 4-dose studies and another for 6-dose studies). The summary table should list the individual study numbers, 28-day efficacy results, study populations, and study location(s). As part of your discussion, it would be useful if you comment on the similarities or differences between the efficacy rates across the studies.
2. Regarding slides in your safety presentation, which present the results for the 4-dose and 6-dose studies side-by-side in the same table, we think presenting the pooled data in this manner encourages cross-study comparisons. As noted in Slide CE-3, you discuss the limitations of the safety reporting in the 4-dose vs. 6-dose studies. We encourage you to change the title of this slide to make it clear you are discussing the limitations of comparing data across studies and to more thoroughly discuss differences in data collection and reporting across studies in the text of the slide. Also, we note it is important to clearly state that in the comparative tables, the two columns (4 dose and 6 dose) should be considered on their own and not compared with each other due to the differences in patient populations, timing of the study, and assessment of adverse events.
3. In general, we notice you do not present any comparative safety information in your slide presentation or briefing book. It might be helpful if you present some comparative safety information obtained from studies utilizing a comparator arm, such as Studies A026 and A028, both of which had MAS as a comparator.
4. The efficacy results for the large pediatric studies, A2403 and B2303, in your slides and briefing book are broken down by body weight, as we requested. We also thought that it may help to provide a more detailed breakdown of the corresponding ages of the children. This will help the audience better understand the population studied, since African children may not weigh the same as U.S. children.
5. In your introductory slides (section CI) please consider discussing why Coartem is being brought to FDA now in 2008, given the fact that it has been approved in other countries for many years and also how the development plan was atypical (i.e., studies were not conducted under IND).

#### Microbiology Comment

6. In your slide presentation, if both uncorrected and corrected cure rates can not be presented simultaneously, it is recommended that only uncorrected cure rates be presented.

Pharmacology/Toxicology Comment

7. In your slide presentation, please include a table illustrating the relationship between the AUC of artemether and the presence of neurodegenerative lesions in the dog studies.

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo

10/21/2008 05:22:51 PM

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NDA 22-268 Facsimile Transmission Additional comments to Applicant from  
October 15, 2008 Division Presentation



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**TRANSMITTAL SHEET**

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**DATE:** October 20, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via Email	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Clinical Pharmacology Information Request-Formulation Concerns

**Total no. of pages including cover:** 3

**Comments: Concurrence**

Philip Colangelo, Ph.D.  
Dakshina Chilukuri, Ph.D.

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**Document to be mailed:**       YES       NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our Clinical Pharmacology review team.

We note in Study 2401 two different formulations (F.4 and F.5) were used in the study patients, therefore please address the following concerns:

1. Please submit a rationale for why two different formulations were used in the study.
2. Please clarify if patients were switched between F.4 and F.5 formulations during the course of the study (3-day dosing regimen).
3. Please submit a table comparing the efficacy of Coartem (primary and secondary endpoints included) for the patients who received F.4 formulation vs. patients who received F.5 formulation.
4. Submit a table comparing the PK estimates (C<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, T<sub>1/2</sub> and T<sub>max</sub>) of lumefantrine in patients who received F.4 vs. F.5 formulations.

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo

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NDA 22-268 Facsimile Transmission Clin/Pharm Formulation Information Reques



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**DATE:** October 10, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via Email	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Information Request from Maternal Health

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**Total no. of pages including cover:** 4

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**Comments:** Concurrence

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our review team. Please note, this information was requested informally in an email communication on October 8, 2008 (see attachment).

- Please submit a paper copy of all the pregnancy registry submission materials.
- Identify the birth defects based on gestational age of exposure during pregnancy, specifically separating out the first trimester exposures.
- Submit an update of the pregnancy registry data since Aug 27, 2007.

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

## Email sent October 8, 2008

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**From:** DiBernardo, Gregory  
**Sent:** Wednesday, October 08, 2008 2:21 PM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** Meyer, Joette M; Willard, Diana M; Sahin, Leyla  
**Subject:** NDA 22-268-Coartem-Novartis- Informal Information Request  
**Importance:** High

Hello Susan,

This email is being sent at this time informally, but an official facsimile transmission requesting this information will follow shortly. We have a request for information to support the review of NDA 22-268, please address the following items as soon as possible.

- Please submit a paper copy for all of the pregnancy registry submission.
- Identify the birth defects based on gestational age of exposure during pregnancy, specifically separating out the first trimester exposures.
- Submit an update of the pregnancy registry data since Aug 27, 2007.

Let me know if you have questions.

Thank you,

**Gregory F. DiBernardo**

Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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/s/

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Gregory F DiBernardo

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NDA 22-268 Facsimile Maternal Health Consult Request for Information



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**TRANSMITTAL SHEET**

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**DATE:** October 10, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via Email	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Clinical Request for Information-Number of Patients in Treatment Groups

**Total no. of pages including cover:** 4

**Comments:** Concurrence

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following request from our Clinical review team. Please note, this information was requested informally in an email communication on September 23, 2008 (see attachment).

In Study 028 (page 36 of clinical trial report) for "Exhibit 8.1-3 (table): Time to parasite clearance."

- **Are the numbers of patients in the two treatment groups correct?**

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Email Sent on September 23, 2008**

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**From:** DiBernardo, Gregory  
**Sent:** Tuesday, September 23, 2008 2:29 PM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** O'Shaughnessy, Elizabeth; Meyer, Joette M  
**Subject:** NDA 22-268-Coartem-Novartis-Quick Clinical Question

Hello Susan,

Please provide a response on the following concern from our Clinical Reviewers. In Study 028 (page 36 of clinical trial report) for "Exhibit 8.1-3 ( table): Time to parasite clearance."

**Are the numbers of patients in the two treatment groups correct?**

Thank you,

**Gregory F. DiBernardo**

Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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Gregory F DiBernardo

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NDA 22-268 Facsimile Clinical Request for Information



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**DATE:** October 10, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via Email	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Information Request to Update Briefing Book and Presentation Slides

**Total no. of pages including cover:** 4

**Comments:** Concurrence

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our review team. These requests primarily focus on the Briefing Book and Presentation slides you submitted to the Division on October 6, 2008 in preparation for your presentation to the Division on October 15, 2008.

1. On page 43 and 45 the briefing book states (b) (4) [REDACTED] Given that these studies (A026 and A028) were not meant as comparative studies and that lack of a significant effect does not imply similarity, we think that both the briefing document and the presentation should not make comparative claims versus MAS.
2. Page 45 is missing a section heading of "Study A028."
3. The term mITT is used often throughout the efficacy section of the briefing book. It appears to only be defined on page 32, where it states, "The mITT population was defined as all randomized patients who received at least one dose of study drug." It also states here that it is newly defined for the pooled analysis, however, it is used to discuss all the studies individually as well. If the term mITT is going to be used instead of the term ITT, it should be defined more often and the number of subjects not receiving at least one dose of study drug should be discussed for each study.
4. We recommend including mention of the drawback with ABMO2 and A023 in that both used only one center and that it was the same center for both studies.
5. The slides on page 187 and 210 states that the 6-dose regimen is superior to the 4-dose regimen. We recommend that if you use the term superior, you should qualify it as only for the evaluable population. Another option would be to say that the cure rates were higher for the 6-dose regimen than the 4 dose regimen.
6. We suggest you consider showing sample size for Evaluable and Intent to treat population in your slide presentation of 28-day cure rate.
7. We note in your pooled safety and efficacy analyses of the 4-dose regimen in adults and/or children that you include results from studies A012, A009, and A011, which use dosing regimens that vary from the other 4-dose studies. Study A012 was a study with 3-treatment arms, two of which (4 x 2 tablets and 3 x 4 tablets) use a lower dose. Please note that we have not included these lower dose groups (3 x 4 and 4 x 2 tablet groups) in our pooled 4-dose adult and pediatric safety population analyses. Studies A009 and A011 use an experimental pediatric tablet formulation, which is half-strength (i.e., 10/60 mg per tablet instead of 20/120 mg). If you choose to include any of these subjects/studies in the pooled safety and efficacy analyses, please make a notation in the text that the dosing regimen used in these studies varies from the proposed regimen and identify the number of subjects exposed to these lower dosing regimens.  
  
Also, please clarify whether or not the studies included in the pooled safety analyses for adults and children are the same as those included in the pooled efficacy analyses for adults and children. Please add information to Section 7.2 of the briefing book to show the studies and the number of subjects from each study contributing to the adult and pediatric safety populations.
8. We note that in your briefing book, the efficacy results for Studies ABMO2, A023, A025, A026, and A028 are provided in tables for adults (>16 years of age) and pediatrics (<=16 years of age) separately. While we requested you present the results separately for these subgroups, please also present the overall study results before reporting the results for the age subgroups. In the tables of overall results please use all the same endpoints as you have done for the age subgroups.
9. Please include a short discussion of the clinical significance of the rapid reduction in parasite counts caused by artemether in the treatment of malaria. Since Coartem is a combination product, it is important to demonstrate the contribution of each of the components to the overall efficacy of the

regimen, as you have done in Studies A023 and ABMO2. In these studies you have shown that Coartem is superior to lumefantrine alone in terms of the early endpoints (i.e., parasite clearance time and parasite reduction at 24 hours). However, Coartem was not significantly different from lumefantrine at the 28-day visit. In Study ABMO2 you have shown that Coartem is similar to artemether in terms of these same early endpoints. Therefore, please include a rationale why the early reduction in parasite count seen with Coartem, and attributed to artemether, is clinically important in treating malaria.

If you have any questions, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo

10/10/2008 11:40:01 AM

CSO

NDA 22-268 Request to Update Briefing Book and Presentation  
Slides



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**TRANSMITTAL SHEET**

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**DATE:** October 9, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via Email	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-CMC Information Request-Drug Substance and Drug Product

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**Total no. of pages including cover:** 6

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**Comments:** Concurrence

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**Document to be mailed:**  YES  NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please completely address the following requests regarding your drug substance (items 1-5) and drug product items (7-12) from our review team. Please expedite your response to **items 12 and 13**. Additionally, items 1-12 were requested informally in an email communication on October 3, 2008, while Item 13 is a new request (see attachment).

1. Please propose an assay test (analytical procedure and acceptance criteria) in the specification of dihydroartemisinin.
2. State if the analytical procedure (HPLC) used for reporting the impurities in the artemether crude and artemether drug substance specifications is capable of detecting the two epimers of dihydroartemisinin and the impurity of the artemisinin starting material, (b) (4)
3. Information provided in section 3.2.S.2.6, Table 2-1. Summary of synthesis modifications includes a statement that the reduction of (b) (4) of artemisinin (at the (b) (4) site) affords (b) (4) of dihydroartemisinin. Please explain this mass balance.
4. Confirm that all the batches of lumefantrine listed in Tables 3.1-3.4 were analyzed for all the impurities listed using the analytical procedure currently proposed for the lumefantrine drug substance. Please provide the limit of detection.
5. Provide information on levels of impurities (other than (b) (4)) observed for batches of lumefantrine manufactured at the (b) (4) facility.
6. Considering very low water solubility of both drugs, please explain if any efforts were made in increasing the drug solubility other than (b) (4) for the development of the tablet formulation.
7. Provide test methods and the data for the compatibility studies of the binary mixtures of the two drugs and excipients.
8. Several unit operations are required in manufacturing the tablets, each with controlled operating parameters (in-process parameters for operating the equipment) and in-process controls (b) (4). Please propose in-process controls for the (b) (4) the currently proposed in-process controls include only (b) (4).
9. Provide data to support the absence of artemether polymorph B in Coartem tablets.
10. Please confirm if a failed batch will be reprocessed or reworked?
11. Include USP disintegration test and specification for Coartem tablets for release and shelf life (we expect to have further comments on the dissolution test).
12. The Division requested the following information in an August 28, 2008 Facsimile:

Identify the same tests in the corresponding validation report by specifying the page number from the Table of Contents for Module 3.2 – Body of Data. (corresponds to the registered and alternate test methods)

You provided a response to this request on September 15th, however because there were no page numbers on the PDF files you submitted in the CMC sections of the original NDA, it is very difficult to locate this information. The page numbers for the validation test methods provided in the September 15<sup>th</sup> submission do not correspond to those pages in the CMC sections of the original NDA submission. Since multiple tests methods are proposed in the drug product specifications for identification, assay, degradation products, and for dissolution testing, it is very difficult to find the corresponding test methods in the validation reports.

**Please expedite your response for the following information:**

For each analytical procedure, including identification, assay, degradation products and dissolution test, provide a combined document containing the proposed analytical procedure and a corresponding validation report.

13. The stability section is compiled from several study reports labeled as registration batches, annual batches, post approval study batches, etc., which appears to be based on studies conducted for registration under a WHO program before this NDA submission. Please provide the following information to expedite review of this data:

Provide page numbers from the original NDA submission for the study protocol, study reports, and stability data for:

Registration Batches for US NDA in (b) (4) bottles with child resistant closures.  
Registration Batches for US NDA in Blister package.  
Supportive Study Batches for US NDA in (b) (4) bottles with or without child resistant closures.  
Supportive Study Batches for US NDA in Blister package.  
Batches used in Statistical analysis of the data. Specify if the batches used for analysis are registration batches or supportive batches.

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Email Sent on October 3, 2008:**

**From:** DiBernardo, Gregory  
**Sent:** Friday, October 03, 2008 10:30 AM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** Willard, Diana M; Pagay, Shrikant N; Matecka, Dorota M; Schmuff, Norman R; 'joan.materna@novartis.com'  
**Subject:** NDA 22-268-Coartem-Novartis- Informal Request for CMC information  
**Importance:** High

Hello Susan,

This email is being sent at this time informally, but an official facsimile transmission requesting this information will follow shortly. Please respond to the items below as soon as you have the information by providing complete responses as a desk copy electronically via email to my attention. However, please remember to submit all responses via an official submission to the Electronic Document Room for this NDA. Our reviewers want you to prioritize **item 12** for this request as it has been requested previously.

Our reviewers have identified the following concerns.

1. Please propose an assay test (analytical procedure and acceptance criteria) in the specification of dihydroartemisinin.
2. State if the analytical procedure (HPLC) used for reporting the impurities in the artemether crude and artemether drug substance specifications is capable of detecting the two epimers of dihydroartemisinin and the impurity of the starting material, (b) (4)
3. Information provided in section 3.2.S.2.6, Table 2-1. Summary of synthesis modifications includes a statement that the reduction of (b) (4) of artemisinin (at the (b) (4) site) affords (b) (4) of dihydroartemisinin. Please explain this mass balance.
4. Confirm that all the batches of lumefantrine listed in Tables 3.1-3.4 were analyzed for all the impurities listed using the analytical procedure currently proposed for the lumefantrine drug substance. Please provide the limit of detection.
5. Provide information on levels of impurities (other than (b) (4)) observed for batches of lumefantrine manufactured at the (b) (4) facility.
6. Considering very low water solubility of both drugs, please explain if any efforts were made in increasing the drug solubility other than (b) (4) for the development of the tablet formulation.
7. Provide test methods and the data for the compatibility studies of the binary mixtures of the 2 drugs and excipients.
8. Several unit operations are required in manufacturing the tablets, each with controlled operating parameters (in-process parameters for operating the equipment) and in-process controls (b) (4) please propose in-process controls for the (b) (4) The currently proposed in-process controls include only (b) (4)
9. Provide data to support the absence of artemether polymorph B in Coartem tablets.
10. Please confirm if a failed batch will be reprocessed or reworked?
11. Include USP disintegration test and specification for Coartem tablets for release and shelf life (we expect to have further comments on the dissolution test).
12. The Division requested the following information in an August 28, 2008 Facsimile:

"Identify the same tests in the corresponding validation method by specifying the page number from the Table of Contents for Module 3.2 – Body of Data." (corresponds to the registered and alternate test methods)

You provided a response to this request on 9/15/08, however because there were no page numbers on the PDF files submitted for with your original CMC NDA submission, it is very difficult to locate this information. The corresponding page numbers for validation test method do not appear to match those in the submission. Since multiple tests methods are proposed in the drug product specifications for identification, assay, degradation products, and for dissolution testing, it is very difficult to find the corresponding validation test methods.

**Please expedite your response for the following information:**

For each analytical procedure, including identification, assay, degradation products and dissolution test, provide a combined document for the proposed test and validation test method.

Please let me know if you have questions.

Thank you,

**Gregory F. DiBernardo**  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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/s/

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Gregory F DiBernardo  
10/9/2008 03:57:53 PM  
CSO

NDA 22-268 Facsimile Transmission CMC Infor Request-Drug Substance and  
Drug Product



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 25, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Information DSPTP would like addressed in Advisory Committee Backgrounder/Briefing Package

**Total no. of pages including cover:** 4

**Comments:**

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**Document to be mailed:**             YES                     NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests from our review team. These requests focus on the Advisory Committee Backgrounder/Briefing Package you previously agreed to provide to the Division in preparation for the upcoming Advisory Committee Meeting on December 3, 2008.

Our reviewers have identified the following concerns they would like to see addressed in the Backgrounder/Briefing Package you plan to submit to the Division on October 3, 2008 and those to be included in your presentation to the Division on October 15, 2008:

### Clinical Efficacy

1. Please present efficacy data separately for patients >16 years of age (adults) and those ≤ 16 years of age (pediatrics).
2. Please focus your discussion of proof of efficacy in terms of the added benefit of each component to the regimen, as well as the added benefit of 6 doses versus 4 doses. The results of the other studies can be more descriptive in nature and should discuss results in specific populations (pediatrics, semi-immune/immune adults, non-immune adults, etc.).
3. Please present and discuss efficacy results in pediatric patients as a function of body weight (pediatric patients stratified as 5-15 kg, 15-25 kg, 25-35 kg, and >35 kg).
4. Please present tables with the following endpoints by treatment arm for each of the eight key studies. As requested in No. 1 above, please provide data for adults and children separately.

Endpoints:

28-day microbiological cure rate (%) [95% CI] in the ITT population
Parasite Clearance Time (median) [95% CI] in ITT population
Fever Clearance Time (median) in patients with fever at baseline
Percent parasite reduction @ 24 hrs (without imputing 0 hours for missing data)
Proportion of patients with parasite reduction of < 75% at 48 hours (i.e., patients not achieving a reduction to < 25% of baseline) in the ITT population
Early Treatment Failure (no. of patients with parasitemia @ 48 hours > baseline) in the ITT population
7 - day microbiological cure rate (%) [95% CI] in the ITT population
Proportion of patients with recrudescence of <i>P. falciparum</i> during the study in the ITT population
Proportion of patients with negative malaria slides at day 2, 3, and 4 in the ITT population

5. (b) (4)

### Clinical Safety

6. Please present safety data separately for patients >16 years of age (adults) and those ≤ 16 years of age (pediatrics).
7. Please include a thorough summary and discussion of your safety findings for “Nervous system disorders” and “Ear and labyrinth disorders”. Note this is in addition to a presentation

and discussion of most frequent AEs, SAEs, deaths and discontinuations for the two pooled safety populations (adults and children).

### **Non-Clinical and Clinical Safety**

8. Please discuss the neurotoxicity findings (histopathologic and behavioral) in animals and relate the exposure and metabolism in animals to the exposure and metabolism in humans. Please also include a discussion of the clinical safety findings from the clinical trials and the post marketing safety database.

### **Microbiology**

9. In your summary of nonclinical studies, you have described the activity of artemisinin. We recommend that you discuss in the background/briefing package the activity and mechanism of action of artemether and DHA.
10. In your tabulation and discussion of efficacy results, please include both uncorrected and corrected cure rates for those studies which utilized PCR genotyping for determination of recrudescence versus new infection.

### **Clinical Pharmacology**

11. Please provide summary tables of mean (+/- SD); range; %CV for PK parameters (AUC, C<sub>max</sub>, T<sub>max</sub>, T<sub>1/2</sub>, CL) of artemether, DHA and lumefantrine for healthy volunteers and patients and a discussion of the PK findings. Present and discuss the PK parameters for adults and pediatric patients separately (pediatric patients stratified as 5-15kg, 15-25 kg, 25-35 kg, and >35 kg).
12. Please provide plots and describe the relationship between clearance of Coartem (artemether, DHA, and lumefantrine) and patient covariates such as body weight and age.
13. Please present and discuss the results of the *in vivo* drug interaction studies of Coartem.
14. Please present and discuss the effect of food on the exposure of Coartem, particularly in the context of the dietary intake of malaria patients. Also, discuss the impact of meal intake on the expected efficacy outcome in malaria patients.

If you have any questions, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo  
9/25/2008 12:35:43 PM  
CSO

NDA 22-268 Facsimile Information Request for Applicant Backgrounder/Briefin



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 16, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Clinical Pharmacology information request-Plots, Tables, and *in vitro* induction of artemether

**Total no. of pages including cover:** 4

**Comments:**

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**Document to be mailed:**             YES                     NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following request for information from our Clinical Pharmacology team. Please note that I originally communicated #1 and #2 listed in this request for information via email to you on September 12, 2008 (see attachment); however, #3 is a new request previously not communicated.

Our Clinical Pharmacology reviewers have identified the following concerns:

1. In order to understand the relationship between Coartem clearance and patient covariates such as body weight and age, please submit the plots listed below for all pediatric patients from all studies where clearance could be estimated. Please submit individual plots for each of the components of Coartem (artemether, DHA, and lumefantrine). Please include trendlines for all the plots.
  - Clearance vs. age
  - Clearance vs. body weight
  - Body-weight normalized clearance vs. age
2. Please submit tables that include PK information for the individual components of Coartem in adult and pediatric patients from all malaria patient studies where PK data were collected. A representation of the requested table is given below.

Steady-state pediatric and adult PK data from all studies that employed the 6-dose regimen

	Cmax (mean ± SD)	AUC (mean ± SD)	Tmax (median and range)	CL (mean ± SD)	T <sub>1/2</sub> (mean ± SD)
5 to <15 kg					
15 to <25 kg					
25 to <35 kg					
>35 kg					
Adults					

**Notes:** Please include N (number of patients) for each parameter

3. Please submit all information, including data pertaining to the *in vitro* induction of artemether.

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Email Sent on September 12, 2008:**


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**From:** DiBernardo, Gregory  
**Sent:** Friday, September 12, 2008 5:06 PM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** Colangelo, Philip M; Chilukuri, Dakshina; Meyer, Joette M; Willard, Diana M  
**Subject:** NDA 22-268-Coartem-Novartis-Clin/Pharm request for information-official fax to follow  
**Importance:** High

Hello Susan,

This email request is being sent at this time informally, but an official facsimile for this request will follow shortly. Please respond to the items below, by providing your responses as a desk copy electronically via email to my attention as soon as they are available. However, please remember to submit all responses via an official submission to the Electronic Document Room for this NDA.

Please submit your official responses to the NDA within two weeks.

Our Clinical Pharmacology reviewers have identified the following concerns:

3. In order to understand the relationship between Coartem clearance and patient covariates such as body weight, and age, we request that you prepare the plots listed below for all pediatric patients from all of the studies in whom clearance could be estimated. Please provide individual plots for each of the components of Coartem (Artemether, DHA and Lumefantrine). Please include trendlines for all the plots.
  - Clearance vs. age
  - Clearance vs. body weight
  - Body-weight normalized clearance vs. age
4. Please submit tables that include PK information of the individual components of Coartem in adult and pediatric patients from all malaria patient studies in which PK data was collected. A representation of the requested table is given below.

Steady-state pediatric and adult PK data from all studies that employed the 6-dose regimen

	Cmax (mean ± SD)	AUC (mean ± SD)	Tmax (median and range)	CL (mean ± SD)	T <sub>1/2</sub> (mean ± SD)
5 to <15 kg					
15 to <25 kg					
25 to <35 kg					
>35 kg					
Adults					

Notes:

1. Please include N (number of patients) for each parameter

Thank you,

**Gregory F. DiBernardo**  
 Regulatory Project Manager  
 Division of Special Pathogen and Transplant Products  
 Office of Antimicrobial Products  
 Center for Drug Evaluation and Research  
 Food and Drug Administration  
 10903 New Hampshire Avenue  
 Building 22, Room 6189  
 Silver Spring, MD 20993  
 Telephone: (301) 796-4063

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/s/

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Gregory F DiBernardo  
9/16/2008 11:53:50 AM  
CSO

NDA 22-268 Facsimile Transmission Clinical Pharmacology Information Request



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 12, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Microbiology information request-Missing Pages Document 51

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**Total no. of pages including cover:** 4

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**Comments:**

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**Document to be mailed:**  YES  NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following request for information from our microbiology team. Please note this request for information was originally communicated via a telephone message and email on September 10, 2008 (see attachment).

Please provide the following material that cannot be located in your October 30, 2007 submission.

- In the Non-Clinical Pharmacology and Toxicology section, under 4.2.1.1-Primary pharmacodynamics, Document 51: Blood schizontocidal activity of Artemether and Benflumetol alone or in combination against *Plasmodium berghei* in *Mus musculus*; Page 12 including Table 3 is missing and Page 17 including Figures 4 and 5 are missing.

Submit the requested information to NDA 22-268; please identify in your cover letter what documents have been submitted.

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Email Sent on September 10, 2008:**

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**From:** DiBernardo, Gregory  
**Sent:** Wednesday, September 10, 2008 4:26 PM  
**To:** susan.kummerer@novartis.com  
**Cc:** Bala, Shukal; Shurland, Simone; Willard, Diana M  
**Subject:** NDA 22-268-Coartem-Novartis-Missing Pages in Doc #51 10/30/07 Non-Clinical submission

Hello Susan,

I left a voice message earlier today regarding missing pages for Document #51 in the 10/30/07 NDA Non-Clinical submission. In this document our reviewer was unable to locate Page 12 including Table 3 and page 17 including Figures 4 & 5. If you could please provide those missing pages with figures and table it would be very helpful. Please inform me when to expect these documents.

At the present time, please submit them via email as an attachment. I will let you know if these material will have to be submitted officially to the NDA.

Thank you,

**Gregory F. DiBernardo**

Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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/s/

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Gregory F DiBernardo  
9/12/2008 10:02:28 AM  
CSO

NDA 22-268 Microbiology Facsimile Request-Missing Pages Document #51



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 12, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Pharmacology/Toxicology information request

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**Total no. of pages including cover:** 3

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**Comments:**

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**Document to be mailed:**  YES  NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following request for information from our Pharmacology/Toxicology team.

- Please provide a data analysis report with interpretation comparing human and dog pharmacokinetics of artemether, including metabolite profiles in plasma. Please include data from all routes of administration available in both humans and dogs, and from both single-dose administration and steady-state data, if available.
- Please clearly identify in your submission the source of the data you use to address this request, including study numbers, the date of submission(s) and location within the submission(s); if not previously submitted, please submit any new documentation you reference to address this request.

Please submit this data analysis and interpretation report to NDA 22-268 by October 3, 2008.

The purpose of this analysis is to better understand the relative exposures of dogs and humans so we can better evaluate the potential for adverse neurologic effects in humans.

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo  
9/12/2008 02:46:48 PM  
CSO

NDA 22-268 Pharm/Tox information request-human & dog PK analysis



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 11, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Clinical Team request for information in response to 9/8/08 submission

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:**             YES                     NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following request for information from our clinical review team. When responding to this request, please reference your September 8, 2008 submission which was in response to the Division's August 15, 2008 facsimile.

- For each data table generated (6-1a, 6-1b, 6-1f for the adult population; 6-2a, 6-2b, 6-2f for the pediatric population), please analyze the data and provide a short summary of your interpretation of these data (i.e., effect, if any, of age, gender, and race on the safety of Coartem).

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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

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Gregory F DiBernardo  
9/11/2008 10:51:32 AM  
CSO

NDA 22-268 Clinical Facsimile Request in response to 9/8/08  
submission

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

<b>Application Information</b>	
NDA # <b>22-268</b>	NDA Supplement #:S- <i>N/A</i> Efficacy Supplement Type SE- <i>N/A</i>
Proprietary Name: <b>Coartem</b> Established/Proper Name: <b>artemether/lumefantrine (pending with USAN)</b> Dosage Form: <b>Tablet</b> Strengths: <b>(20 mg artemether /120 mg lumefantrine) combination</b>	
Applicant: <b>Novartis Pharmaceuticals Corporation</b> Agent for Applicant (if applicable): <i>N/A</i>	
Date of Application: <b>6/27/08</b> Date of Receipt: <b>6/27/08</b> Date clock started after UN: <i>N/A</i>	
PDUFA Goal Date: <b>12/27/08</b>	Action Goal Date (if different): <b>12/22/08</b>
Filing Date: <b>8/26/08 (60 days)</b> Date of Filing Meeting: <b>8/5/08</b>	
Chemical Classification: (1,2,3 etc.) (original NDAs only) <b>Type 1</b>	
Proposed Indication(s): <b>Treatment of infections due to <i>Plasmodium falciparum</i> or mixed infections including <i>P. falciparum</i></b>	
Type of Original NDA: <b>7/15/08 356h states type</b> AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Type of NDA Supplement: <i>N/A</i> <b>Refer to Appendix A for further information.</b>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted <input checked="" type="checkbox"/> Not applicable
Resubmission after withdrawal? <input type="checkbox"/> <input checked="" type="checkbox"/> Not applicable Resubmission after refuse to file? <input type="checkbox"/> <input checked="" type="checkbox"/> Not applicable	
Part 3 Combination Product? <input type="checkbox"/> <input checked="" type="checkbox"/> Not applicable	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device
<input checked="" type="checkbox"/> Fast Track: <b>Granted 1/14/08</b> <input checked="" type="checkbox"/> Rolling Review: <b>Granted 1/14/08</b> <input checked="" type="checkbox"/> Orphan Designation: <b>Granted 8/31/07</b>  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other: <b>These items are N/A</b>	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product): <input checked="" type="checkbox"/> Not applicable	

List referenced IND Number(s): <b>PIND 75,287</b>	
PDUFA and Action Goal dates correct in tracking system? <b>DRTL Emailed 8/6/08 to change to 12/27/08</b> <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <b>USAN Application submitted 6/11/08.</b> <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <b>Potential changed to "Priority" 8/7/08</b> <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aip.html">http://www.fda.gov/ora/compliance_ref/aip.html</a>  <b>If yes, explain:</b>  <b>If yes, has OC/DMPQ been notified of the submission?</b>  <b>Comments:</b> <i>N/A</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted <b>Submitted 10/29/07</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  <b>Comments: Orphan Designation granted in 8/31/07 letter</b>	<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  <b>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</b>  <i>If yes, consult the Director, Division of Regulatory Policy II,</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Office of Regulatory Policy (HFD-007)</i>  <b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments: 5 year Waxman-Hatch exclusivity requested in letter dated 07/24/08.</b></p>	<p><input checked="" type="checkbox"/> YES  # years requested: <b>5</b>  <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	
<p><b>7/15/08 form 356h states 505(b)(1)</b></p> <ol style="list-style-type: none"> <li>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</li> <li>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</li> </ol> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b></p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>																	
<p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>		Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																	
<p><b>Format and Content</b></p>																	
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments: Application submitted in eNDA form.</b></p> <p><input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)</p> <p><input type="checkbox"/> CTD <input checked="" type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)</p>																	
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>	<p>N/A</p>																
<p><b>If electronic submission:</b> paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments: Applicant informed Division no Pediatric Certification was submitted, they have Orphan Designation.</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>																
<p><b>If electronic submission</b>, does it follow the eCTD guidance? (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not</b>, explain (e.g., waiver granted): <b>No waiver was officially granted for this NDA as Novartis, began submission of their step-wise NDA submission prior to a wavier being necessary for non-eCTD submissions. The applicant did submit a request to file eNDA and this was granted on 12/21/07. The applicant states having a wavier from a letter dated 2/11/08.</b></p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>																

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b> Applicant omitted some key information from form 356h submitted on 6/27/08. They were contacted and on 7/15/08 they submitted an updated version. On 5/14/08 Drug Substance (DS) information was submitted, on 6/26/08 Drug Product (DP) information was submitted. The establishments and their registration numbers for both DS &amp; DP were submitted as an attachment on 6/26/08 indicted on 6/26/08 form 356h.</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b> An integrated table of contents was submitted with each piece of the step-wise NDA submission. A comprehensive table of contents for the submission was submitted on 7/21/2008 however, the PM had to modify it to fit reviewers needs.</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b> CMC Drug Substance and Drug Product did not have pagination for this part of submission the CMC Branch Chief was able to resolve this issue.</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO

If yes, BLA #	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
Patent information submitted on form FDA 3542a?  <b>Comments: Submitted 6/27/08</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
Correctly worded Debarment Certification with authorized signature?  <i>If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>  <b>Comments: Submitted 6/27/08</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
Field Copy Certification: that it is a true copy of the CMC technical section ( <i>applies to paper submissions only</i> )  <b>Submitted 6/26/08</b>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/> Not Applicable ( <i>electronic submission or no CMC technical section</i> ) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Financial Disclosure</b>	
Financial Disclosure forms included with authorized signature?  <i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>  <b>Comments: Submitted 6/27/08</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Pediatrics</b>	
<b>PREA</b>	
<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	
Are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES

<p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li><i>If no, request in 74-day letter.</i></li> <li><b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul> <p><b>Comments: Orphan Designation-Exempt from PREA</b></p>	<input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Prescription Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments: Submitted 6/27/08</b></p>	<input type="checkbox"/> <b>Not applicable</b> <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments: Submitted 6/27/08</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Package insert (PI) submitted in PLR format?</p> <p><b>If no</b>, was a waiver or deferral requested before the application was received or in the submission?  <b>If before</b>, what is the status of the request?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments: Submitted 6/27/08</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p><b>Comments: Consult request sent 8/7/08</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send</i></p>	<input checked="" type="checkbox"/> Not Applicable

WORD version if available)	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments: DMEPA consulted on 8/1/07 for Proprietary Name Review. On 6/24/08 a 2<sup>nd</sup> consult was requested to examine the Applicant's response to DMEPA recommendations from 8/1/07 consult. OSE Consult request for PI, carton and immediate container labels sent 8/8/08.</b>	

<b>OTC Labeling</b>	
Check all types of labeling submitted.	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<b>Comments:</b>	
Is electronic content of labeling submitted?	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> YES <input type="checkbox"/> NO
<i>If no, request in 74-day letter.</i>	
<b>Comments:</b>	
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> YES <input type="checkbox"/> NO
<i>If no, request in 74-day letter.</i>	
<b>Comments:</b>	
If representative labeling is submitted, are all represented SKUs defined?	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> YES <input type="checkbox"/> NO
<i>If no, request in 74-day letter.</i>	
<b>Comments:</b>	
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
<b>Meeting Minutes/SPA Agreements</b>	

<p>End-of Phase 2 meeting(s)?  <i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments: This product came into Division as a PIND 8/25/06, then became a step-wise NDA submission on 1/14/08, finally becoming an NDA on 6/27/08.</b></p>	<p><input type="checkbox"/> YES  Date(s):  <input checked="" type="checkbox"/> NO</p>
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?  <i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments: Pre-IND/Pre-NDA meeting 11/09/07</b></p>	<p><input checked="" type="checkbox"/> YES  Date(s): November 9, 2008  <input type="checkbox"/> NO</p>
<p>Any Special Protocol Assessment (SPA) agreements?  <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES  Date(s):  <input checked="" type="checkbox"/> NO</p>

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** August 5, 2008

**NDA #:** 22-268

**PROPRIETARY/ESTABLISHED NAMES:** Coartem, (artemether/lumefantrine)

**APPLICANT:** Novartis Pharmaceuticals Corporation

**BACKGROUND:** Coartem (artemether/lumefantrine) Tablet is a new Molecular Entity with the indication of treatment of infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. The applicant was granted Rolling Review and Fast Track Designation on January 14, 2008; applicant also given Orphan Designation on August 31, 2007. It is licensed in approximately 80 countries outside of the United States as Coartem/Riamet.

*(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)*

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	<b>Gregory DiBernardo</b>	Y
	CPMS/TL:	<b>Diana Willard</b>	N
Cross-Discipline Team Leader (CDTL)	<b>Joette Meyer, Pharm.D.</b>		Y
Clinical	Reviewers:	<b>Elizabeth O'Shaughnessy, M.D. (Efficacy)</b> <b>Sue Lim, M.D. (Safety)</b> <b>Ozlem Belen, M.D. (Pediatric Safety)</b>	Y Y-call-in N
	TL:	<b>Joette Meyer, Pharm. D.</b>	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
OSE	Reviewers:	<b>Denise V. Baugh, Pharm. D. (Trade Name)</b>	Y

		<b>(Label)</b>	
	TL:	<b>Linda Y. Kim-Jung, Pharm.D. (Trade Name) (Label)</b>	N
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	<b>Aaron Ruhland, Ph.D. Simone Shurland, Ph.D.</b>	Y N
	TL:	<b>Shukal Bala, Ph.D.</b>	N

Clinical Pharmacology	Reviewer:	<b>Dakshina Chilukuri, Ph.D</b>	Y-call-in
	TL:	<b>Philip Colangelo, Ph.D.</b>	Y
Biostatistics	Reviewer:	<b>Xianbin Li, Ph.D. Lan Zeng, Ph.D.</b>	Y N
	TL:	<b>Karen Higgins, Ph.D.</b>	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	<b>Rama Dwivedi, Ph.D. Stephen Hundley, Ph.D. Owen McMaster, Ph.D.</b>	Y Y N
	TL:	<b>William Taylor, Ph.D.</b>	Y
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	<b>Dorota Matecka, Ph.D. Shrikant Pagay, Ph.D.</b>	Y Y
	TL:	<b>Norman Schmuff, Ph.D.</b>	Y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:	N/A	
	TL:	N/A	
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (DSI)	Reviewer:	<b>Susan Thompson, M.D.</b>	Y
	TL:	<b>Tejashri Purohit-Sheth, M.D.</b>	N
Other reviewers	<b>QT-IRT Reviewer to be named DDMAC Reviewer to be named OSE Label Reviewer to be named</b>		N N N

**OTHER ATTENDEES:** Edward Cox M.D., Director, OAP, David Roeder Associate Director of Regulatory Affairs, OAP, Judit Milstein CPMS DSPTP, Darrell Jenkins OSE, Janie Kim, Pharm.D., Advisors and Consultants (call-in), Karen Templeton-Somers, Ph.D., Supervisory Team Leader, ACS (call-in), Melanie Brinkley DSPTP, June Germain DSPTP, Sherry Spriggs DSPTP, Tafadzwa Vargas-Kasambira M.D., DSPTP

<p>505(b)(2) filing issues?</p> <p><b>If yes, list issues:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>Per reviewers, are all parts in English or English translation?</p> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b> eNDA submission presented some difficulty at times in locating materials within the submission and there was no pagination for CMC drug product and substance submissions. Complete Table of Contents submitted by the applicant for the NDA was not as effective as a tool as review team needed so an in house Table of Contents was created to meet this need.</p>	<p><input type="checkbox"/> Not Applicable</p>
<p><b>CLINICAL</b></p> <p><b>Comments:</b> An email was sent informally to applicant to communicate Clinical review issues on 8/5/08, then an official facsimile was sent on 8/7/08 to communicate these same concerns.</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical study site(s) inspections(s) needed?</p> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>• Advisory Committee Meeting needed?</p> <p><b>Comments:</b> DSI Consult submitted 7/17/08, site inspections to begin at selected site the last week of September or 1<sup>st</sup> week of October 2008.</p> <p><b>If no, for an original NME or BLA application, include the reason. For example:</b></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> </ul>	<p><input checked="" type="checkbox"/> YES  Date if known: <b>December 3, 2008</b>  <input type="checkbox"/> NO  <input type="checkbox"/> To be determined</p> <p>Reason:</p>

<ul style="list-style-type: none"> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>● If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b> Review of NDA will be a joint review, with one reviewer examining non-clinical data and the other reviewing clinical data. Microbiology team may have labeling concerns, but will need to await applicant's response to 7/9/08 facsimile.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Applicant sent email on 8/1/08, followed by official facsimile on 8/7/08 to request the location of the full study report for the exposure-response (E-R) analysis listed under the PK portion of the Study report CCOA566A025; since review team could not find this material. May have comment for 74-day letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>● Clinical pharmacology study site(s) inspections(s) needed?</li> <li>● They do not foresee a need for inspections, but will update PM if there is a change.</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIostatistics</b></p> <p><b>Comments:</b> Explained design of the studies submitted, the ranking of the 8 key clinical studies used in the NDA review, and the breakdown of the 4 dose vs. 6 dose studies. No comments for 74-day letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL</b></p>	<input type="checkbox"/> Not Applicable

<p><b>(PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> Reviewer discussed neurotoxicity issues seen in dog studies at high dose levels when given in intramuscular formulation. Reviewer informed team this finding was not seen with the oral formulation. The Pharmacology/Toxicology team had no review issues for 74-day letter at this time.</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Review of NDA will be a joint review, with one reviewer examining Drug Product data and the other reviewing Drug Substance data. No comments for 74-Day letter at this time, but may have comments to be sent to applicant.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments: Applicant providing justification to not submit EA, if deemed acceptable by CMC team, then no need for a consult to be requested.</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments: Facsimile request sent 8/14/08 for confirmation that establishments are ready for inspection.</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Sterile product? Drug Product is a tablet.</li> </ul> <p><b>If yes</b>, was Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority: Edward Cox, M.D.</b>	
<b>GRMP Timeline Milestones:</b> Sign off/Action date of 12/22/08 proposed	
<b>Comments:</b> Labeling Discussions to begin 11/17/08	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If BLA or priority review NDA, <b>send 60-day letter.</b>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Denise Baugh, Pharm.D, from DMEPA provided an update on the 6/24/08 Consult request to examine the Applicant's appeal of DMEPA's recommendations from April 15, 2008 Consult. She indicated that DMEPA still does not recommend the use of the Proprietary name Coartem.

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

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Gregory F DiBernardo

9/9/2008 10:28:36 AM

CSO

NDA 22-268 Regulatory Filing Review & Filing Meeting Memo

505(b)(2) ASSESSMENT

Application Information		
NDA # <b>22-268</b>	NDA Supplement #:S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: <b>Coartem</b> Established/Proper Name: <b>artemether/lumefantrine</b> Dosage Form: <b>Tablet</b> Strengths: <b>20 mg/120 mg combination</b>		
Applicant: <b>Novartis Pharmaceuticals Corporation</b>		
Date of Receipt: <b>June 27, 2008</b>		
PDUFA Goal Date: <b>December 27, 2008</b>		Action Goal Date (if different): <b>December 22, 2008</b>
Proposed Indication(s): <b>Treatment of infections due to <i>Plasmodium falciparum</i> or mixed infections including <i>P. falciparum</i></b>		

**GENERAL INFORMATION**

1. Is this application for a drug that is an “old” antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES  NO

*If “YES,” proceed to question #3.*

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES  NO

*If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
<b>Not Applicable</b>	<b>Not Applicable</b>

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)  
**Not Applicable**

**RELIANCE ON PUBLISHED LITERATURE**

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #6.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #6*

*If “YES”, list the listed drug(s) identified by name and answer question #5(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.*

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #11.*

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

YES  NO

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

9. Were any of the listed drug(s) relied upon for this application:

- a. Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b. Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c. Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d.1.

If "NO", proceed to question #10.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If "YES" and there are no additional pharmaceutical equivalents listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "NO", proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):



**PATENT CERTIFICATION/STATEMENTS**

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **Not Applicable**

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s): **Not Applicable**

15. Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s):

*If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?*

YES  NO

*Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.*

YES  NO

Date Received:

*Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.*

YES  NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

*If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?*

YES  NO

*Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.*

YES  NO

Date Received:

*Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.*

YES  NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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this page is the manifestation of the electronic signature.**  
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/s/

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Gregory F DiBernardo  
9/9/2008 10:35:48 AM  
CSO  
(b)(2) Assessment Form NDA 22-268



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your new drug application (NDA) dated June 27, 2008, received June 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets. In agreement with our January 14, 2008 letter, this NDA was submitted in a step-wise manner beginning October 30, 2007.

We also refer to the following information that identifies the step-wise submissions of your NDA, prior, to your June 27, 2008 submission and those submissions that followed the June 27, 2008 submission:

October 30, 2007	April 18, 2008	May 22, 2008	June 5, 2008
February 11, 2008	April 22, 2008	May 23, 2008	June 10, 2008
February 27, 2008(2)	May 9, 2008 (2)	May 29, 2008	June 16, 2008
March 19, 2008	May 15, 2008	June 2, 2008	June 19, 2008
March 20, 2008	May 16, 2008	June 4, 2008	June 26, 2008
April 8, 2008			
July 1, 2008	July 15, 2008	July 24, 2008	August 18, 2008
July 2, 2008 (3)	July 17, 2008	August 5, 2008	August 19, 2008
July 3, 2008	July 21, 2008	August 7, 2008	August 21, 2008
July 8, 2008	July 22, 2008	August 8, 2008	August 22, 2008
July 9, 2008	July 23, 2008 (2)	August 15, 2008 (2)	August 28, 2008

During our filing review of your application, we identified the following potential review issues:

1. A detailed summary of the existing worldwide post-marketing safety data available for Coartem/Riamet cannot be found in the application. Please provide the following:
  - The number of reports; list of countries which have provided data; list of the Health Authorities which report to this database; list and summarize all post-marketing studies which have been performed.

- In Section 4.4.2 of the Clinical Overview, evidence from published data is summarized for efficacy alone. Please summarize the safety data from these published studies.
- Please provide a listing of all known SAEs from the worldwide post marketing database. Please include as much additional details as possible, e.g. narratives (if available), summaries.
- Please provide a listing of all AEs of severe intensity from the worldwide post marketing database. Please include as much additional details as possible, e.g. narratives (if available), summaries.
- It is noted that “since the original approval, and based on post marketing data, the following events have been added to the “Undesirable Effects section of the labeling” and AEs for Adults and adolescents, and for Infants and children are listed. Please clarify the following:
  - To which country(ies) label(s) have these AEs been added?
  - What was the basis/rationale for adding each of these events to the label? Please include the number of cases, country of report origin, severity of the AE and any other relevant information

Please ensure the following when submitting the above data:

- provide all post marketing AE reports regardless of causality
- report AEs by their relevant System Organ Class (SOC) and Preferred Term (PT)
- organize and report post marketing AE data in the same fashion as the reporting of safety data, namely in the following pooled populations: adults and adolescents (>16 years of age); elderly (≥ 65 years); and pediatrics (≤ 16 years).

Finally, please ensure that the summary of post-marketing data includes all published safety information, including that which comes from case reports, case series, etc. of adverse events and which may not be covered by the second bullet point above (i.e., clinical efficacy studies).

2. The Coding Dictionary submitted as part of your August 15, 2008 submission is not sufficient to allow for an in-depth review of this NDA. Provide a listing of all investigator verbatim terms and the preferred terms to which they were mapped. It would be most helpful if you submit this as an SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim). Again, refer to the Division’s August 19, 2008 facsimile request for thorough details.
3. The annotated product labeling within the microbiology section (sections 12.1 and 12.2), does not link to study reports. For example, in Section 12.2 it is stated that “strains of *P. falciparum* with a moderate decrease in susceptibility to artemether or lumefantrine alone can be selected *in vitro* or *in vivo*.” However, there are no links to the reports that define these phenomena both *in vitro* and *in vivo*. A detailed annotation, with complete linking functions, is needed for these sections.
4. Please provide a table listing analysis and impurity levels, identifying lots of the drug substances and the drug product used in preclinical and clinical studies, etc. as described in ICH Q3A/Q3B guidances. Please use two tables similar to the ones below for drug substance and drug product batches:

Batch ID #	Date of Manufacture	Batch size	Manufacturing Process	Manufacturing Site	Analytical Procedure
XXXX					
YYYY					
ZZZZ					

Drug Substance Batch	XXXX	XXXX
Drug Product Batch	----	YYYY
Use	Nonclinical	Clinical
Study #		
Assay observed (proposed acceptance criteria)		
Impurity 1 observed amount (proposed acceptance criteria)		
Impurity 2 observed amount (proposed acceptance criteria)		
Total Other Impurities observed (proposed acceptance criteria)		

- Please provide information regarding your supplier qualification procedures and controls for pesticides, herbicides, and residual solvents for artemisinin.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. The timeliness of your responses is critical to ensure the Division has sufficient time to thoroughly review material in this review cycle. Submit complete responses to all items (1-9) listed in this letter no later than September 16, 2008, particularly requests made last month.

We also request that you submit the following information:

- Please provide complete responses to all the items listed above as potential review issues, remember to submit your responses officially to your NDA.
- Complete responses to all items requested in the Division's August 15, 2008 Clinical facsimile request.
- Complete responses to all items requested in the Division's August 28, 2008 CMC facsimile request.

9. Complete responses to all items requested in the Division's August 29, 2008 Statistical facsimile request.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

-----  
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/s/

-----  
Renata Albrecht  
9/8/2008 05:02:25 PM



NDA 22-268

**PRIORITY REVIEW DESIGNATION**

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your new drug application (NDA) dated June 27, 2008, received June 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the following submissions wherein sections of this NDA were submitted step-wise, in accordance with our January 14, 2008 letter, to your June 27, 2008 submission:

October 30, 2007	April 18, 2008	May 22, 2008	June 5, 2008
February 11, 2008	April 22, 2008	May 23, 2008	June 10, 2008
February 27, 2008(2)	May 9, 2008 (2)	May 29, 2008	June 16, 2008
March 19, 2008	May 15, 2008	June 2, 2008	June 19, 2008
March 20, 2008	May 16, 2008	June 4, 2008	June 26, 2008
April 8, 2008			

In addition, we refer to the following submissions that were reviewed and considered for the filing of this application:

July 1, 2008	July 15, 2008	July 24, 2008	August 18, 2008
July 2, 2008 (3)	July 17, 2008	August 5, 2008	August 19, 2008
July 3, 2008	July 21, 2008	August 7, 2008	August 21, 2008
July 8, 2008	July 22, 2008	August 8, 2008	August 22, 2008
July 9, 2008	July 23, 2008 (2)	August 15, 2008 (2)	

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days

after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is December 26, 2008.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 9, 2008.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

-----  
Renata Albrecht  
8/26/2008 07:04:15 PM



NDA 22-268

**PRIORITY REVIEW DESIGNATION**

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your new drug application (NDA) dated June 27, 2008, received June 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the following submissions wherein sections of this NDA were submitted stepwise, in accordance with our January 14, 2008 letter, to your June 27, 2008 submission:

October 30, 2007	April 18, 2008	May 22, 2008	June 5, 2008
February 11, 2008	April 22, 2008	May 23, 2008	June 10, 2008
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March 19, 2008	May 15, 2008	June 2, 2008	June 19, 2008
March 20, 2008	May 16, 2008	June 4, 2008	June 26, 2008
April 8, 2008			

In addition, we refer to the following submissions that were reviewed and considered for the filing of this application:

July 1, 2008	July 15, 2008	July 24, 2008	August 18, 2008
July 2, 2008 (3)	July 17, 2008	August 5, 2008	August 19, 2008
July 3, 2008	July 21, 2008	August 7, 2008	August 21, 2008
July 8, 2008	July 22, 2008	August 8, 2008	August 22, 2008
July 9, 2008	July 23, 2008 (2)	August 15, 2008 (2)	

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days

after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is December 26, 2008.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 9, 2008.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Renata Albrecht  
8/26/2008 07:04:15 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): **Maternal Health Staff**  
Attention: **Tammie Brent-Steele, PM**

FROM (Name, Office/Division, and Phone Number of Requestor): **Gregory DiBernardo, PM/ Joette Meyer, Acting Clinical Team Leader, DSPTP/(301) 796-4063**

DATE  
August 20, 2008

IND NO.

NDA NO.  
22-268

TYPE OF DOCUMENT  
Product Label

DATE OF DOCUMENT  
June 27, 2008

NAME OF DRUG  
**Coartem (proposed)**  
(artemether/lumefantrine)

PRIORITY CONSIDERATION  
Priority

CLASSIFICATION OF DRUG  
Antimalarial (4050120)

DESIRED COMPLETION DATE  
October 20, 2008

NAME OF FIRM: **Novartis Pharmaceuticals Corporation**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** We are requesting a consult review of the proposed product label for Coartem (proposed trade name) as well as the human data provided in the pregnancy registry. Please note, the applicant did not agree with the recommendations from the 4/15/08 proprietary name review completed under PIND 75,287 and appealed the recommendations made by DMEPA, for which a second consult was requested. Therefore, the name Coartem listed on the product label may change as this NDA progresses through the review cycle. Please note that the Annotated Label can be found in the Summary Folder (it is not in the Labeling Folder). The EDR link for the labeling information can be found at: \\FDSWA150\NONECTD\N22268\N\_000\2008-06-27

The label states that Coartem (b) (4)

(b) (4)

[REDACTED] The applicant indicated that they have a pregnancy registry and have provided interim data from the registry in the NDA. We would also like a review of these human data the applicant has provided. This information can be found in the EDR by following this link:

\\Fdswwa150\NONECTD\N22268\R\_011\2008-05-09

Coartem is an NME and a combination antimalarial drug (artemether and lumefantrine, also known as benflumetol) being developed for the treatment of acute, uncomplicated malaria in adults and children due to P. falciparum. The application has been granted a Priority review (PDUFA goal date of December 27, 2008) and has Orphan Designation. Also, since this is an NME, it will be discussed at an Advisory Committee meeting (per FDAAA) scheduled for December 3, 2008.

If you have any questions, please forward them to DSPTP.  
Thank you.

SIGNATURE OF REQUESTOR

Gregory DiBernardo

METHOD OF DELIVERY (Check one)

DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Gregory F DiBernardo  
8/20/2008 12:23:28 PM  
NDA 22-268 Maternal Health Team Consult Request for Product  
Label and Human Data



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 19, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Clinical Team request for information

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**Total no. of pages including cover:** 4

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**Comments:**

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**Document to be mailed:**  YES  NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests for information from our Clinical review team.

Information requests 1-5 pertain to response #1 (re: worldwide post marketing safety data available for Coartem) from your August 15, 2008 submission, which was in response to the Division's July 29, 2008 facsimile.

1. Please provide the following additional details on your worldwide database for Coartem: number of reports; list of countries which have provided data; list of the Health Authorities which report to this database; list and summarize all post marketing studies which have been performed.
2. In Section 4.4.2 of the Clinical Overview, evidence from published data is summarized for efficacy alone. Please summarize the safety data from these published studies.
3. Please provide a listing of all known SAEs from the worldwide post marketing database. Please include as much additional detail as possible, e.g. narratives (if available), summaries.
4. Please provide a listing of all AEs of severe intensity from the worldwide post marketing database. Please include as much additional detail as possible, e.g. narratives (if available), summaries.
5. In response #1, it is noted that "since the original approval, and based on post marketing data, the following events have been added to the Undesirable Effects section of the labeling", and AEs for Adults and adolescents, and for Infants and children are listed. Please clarify the following:
  - To which country(ies) label(s) have these AEs been added?
  - What was the basis/rationale for adding each of these events to the label? Please include the number of cases, country of report origin, severity of the AE and any other relevant information

Please ensure the following when submitting data for #2, 3 and 4 above:

- please provide all post marketing AE reports regardless of causality
- please report AEs by their relevant System Organ Class (SOC) and Preferred Term (PT)
- please organize and report post marketing AE data in the same fashion as the reporting of safety data, namely in the following pooled populations: adults and adolescents (>16 years of age); elderly ( $\geq$  65 years); and pediatrics ( $\leq$  16 years).

The following information request pertains to response #2 (re: location of the coding dictionary used for all studies) which was provided in the same August 15, 2008 NDA submission.

6. Please note that the information you provided does not address our request. When we refer to the "coding dictionary", we are looking for a listing of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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Gregory F DiBernardo  
8/19/2008 04:25:24 PM  
CSO

NDA 22-268 Facsimile Transmission Request for Clinical Information



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 15, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Clinical Team request for information

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**Total no. of pages including cover:** 4

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**Comments:**

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**Document to be mailed:**             YES                     NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests for information from our Clinical review team.

1. Tables 5-31 and 5-32 of the Clinical Overview show Serious AEs in the adult and adolescent, and pediatric pooled safety populations respectively. Please submit 2 tables in the same format (i.e. AEs reported by both Primary system organ class and preferred term, and stratified according to 4-dose, 6-dose, total, MAS or SP): One table should contain all AEs in the adult and adolescent population (defined as patients > 16 years) and the second table should contain all AEs in the pediatric population (defined as patients ≤ 16 years).
2. From these two tables which are already stratified according to Coartem dose or comparator, please perform subgroup analyses for all AE preferred terms >1% of any group according to the following factors:
  - a. **Age:** for the pediatric population, please use the following categories: 0 to ≤ 2 years; >2 to ≤ 6 years; >6 to ≤ 12 years; >12 to ≤ 16 years; and 0 to ≤ 16 years inclusive. For the adult and adolescent population, please analyze according to age >16 to ≤ 65 years, and age greater than 65 years
  - b. **Gender**
  - c. **Race**

These subgroup analyses should be presented in the following format (gender subgroup analysis in the adult pooled population shown as an example):

n (%) patients								
Co-artemether								
Primary system organ class Preferred term	4-dose N=1098		6-dose N=712		Total N=1810		MAS N=352	
	Male	Female	Male	Female	Male	Female	Male	Female
Blood and lymphatic system disorders Thrombocytopenia								

3. Please provide a rationale for why most of the more common AEs were seen more frequently with the 4-dose Coartem regimen compared to the 6-dose regimen.
4. We note in your table of contents (submission letter date April 18, 2008 “NDA Presubmission – Additional clinical study reports”) that you have included reports for Studies IC04 “Cameroon Open, multicenter, comparative safety and efficacy study of Coartem in malaria patients” and IC04 “Senegal Open, multicenter comparative safety and efficacy study of Coartem in malaria patients” in the NDA submission. Please explain why these studies were not included in the pooled safety or efficacy analyses.

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

-----  
Gregory F DiBernardo  
8/15/2008 10:33:19 AM  
CSO

NDA 22-268 Facsimile Transmission Request for Clinical Information SAE  
& AE

## REQUEST FOR CONSULTATION

TO (Office/Division): **Office of Surveillance and Epidemiology (OSE) Attention: Darrell Jenkins, RPM**

FROM (Name, Office/Division, and Phone Number of Requestor): **Gregory DiBernardo, PM/ Joette Meyer, Acting Clinical Team Leader, DSPTP/(301) 796-4063**

DATE  
August 8, 2008

IND NO.

NDA NO.  
22-268

TYPE OF DOCUMENT  
Package Insert, Carton  
and Container Labels

DATE OF DOCUMENT  
June 27, 2008

NAME OF DRUG  
Coartem (proposed)  
(artemether/lumefantrine)

PRIORITY CONSIDERATION  
Priority

CLASSIFICATION OF DRUG  
Antimalarial (4050120)

DESIRED COMPLETION DATE  
October 3, 2008

NAME OF FIRM: **Novartis Pharmaceuticals Corporation**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** We are requesting a consult review for the carton and container labels and the package insert for Coartem (proposed trade name). Please note, the applicant did not agree with the recommendations from the 4/15/08 proprietary name review completed under PIND 75,287 and appealed the recommendations made by DMEPA. Therefore, the name Coartem listed on the package insert, carton, and container labels may change as this NDA progresses through the review cycle. The EDR link for the labeling information is: \\FDSWA150\NONECTD\N22268\N\_000\2008-06-27

Please note that the Annotated Label can be found in the Summary Folder (it is not in the Labeling Folder).

Coartem is an NME and a combination antimalarial drug (artemether and lumefantrine, also known as benflumetol) being developed for the treatment of acute, uncomplicated malaria in adults and children due to *P. falciparum*. The applicant has been granted a Priority review, which means a PDUFA goal date of December 27, 2008.

Also, since this is an NME, it will be discussed at an Advisory Committee meeting (per FDAAA) scheduled for

December 3, 2008.

Please forward any comments that you have for this consult to the DSPTP.

Thank you for your help.

SIGNATURE OF REQUESTOR

Gregory DiBernardo

METHOD OF DELIVERY (Check one)

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/s/

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Gregory F DiBernardo  
8/8/2008 04:57:32 PM  
NDA 22-268 OSE Consult Request For Package Insert ,  
Carton Labeling & Container Packaging



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 7, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Clinical request for information

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**Total no. of pages including cover:** 4

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**Comments:**

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**Document to be mailed:**             YES                     NO

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following requests for information from our Clinical team. Please note this request for information was originally communicated informally via an Email on August 5, 2008 (see attachment).

Your response to our request should be submitted as an official amendment to the NDA.

1. Provide the formats for the Pooled data sets in the form of a .sas7bcat catalog file (Currently it appears as "d\_fmtdat.sas7bdat")
2. For the 8 key studies, please submit:
  - i) A pooled dataset for concomitant medications. Please set this dataset up in the same format as Study B2303.
  - ii) A pooled dataset for past medical history. Please set this dataset up in the same format as Study 2401.
  - iii) A pooled dataset for body temperature. We are interested in looking at body temperature readings at different time points across studies. Please keep results for adults and children separate.
3. For the "A\_IDENT" dataset, please add a variable which indicates if the subject received "Coartem" or "comparator".
4. In the clinical study report for Study BD01 it states (on page 12 of the study report) that the classification of therapeutic response can be found in appendix 4. We were not able to locate appendix 4. Therefore, please provide the definition of therapeutic response used in this study.

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

## Email Sent on 8/5/08

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**From:** DiBernardo, Gregory  
**Sent:** Tuesday, August 05, 2008 1:55 PM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** Meyer, Joette M; O'Shaughnessy, Elizabeth; Lim, Sue; Cooper, Charles (CDER); Willard, Diana M  
**Subject:** NDA 22-268-Coartem-Novartis-Clinical Information Request

Hello Susan,

This email is being sent at this time informally, but an official facsimile will follow shortly. Please respond to #1 below, by providing your comments as a desk copy electronically via email to my attention. However, please remember to submit all responses via an official submission to the Electronic Document Room for this NDA.

Our Clinical reviewers have identified the following concerns:

1. **Provide the formats for the Pooled data sets in the form of a .sas7bcat catalog file (Currently it appears as "d\_fmtdat.sas7bdat")**
2. For the 8 key studies, please submit:
  - i) A pooled dataset for concomitant medications. Please set this dataset up in the same format as Study B2303.
  - ii) A pooled dataset for past medical history. Please set this dataset up in the same format as Study 2401.
  - iii) A pooled dataset for body temperature. We are interested in looking at body temperature readings at different time points across studies. Please keep results for adults and children separate.
3. For the "A\_IDENT" dataset, please add a variable which indicates if the subject received "coartem" or "comparator".
4. In the clinical study report for Study BD01 it states (on page 12 of the study report) that the classification of therapeutic response can be found in appendix 4. We were not able to locate appendix 4. Therefore, please provide the definition of therapeutic response used in this study.

Susan, please make **#1 a priority** as this data is quite important to the reviewers at this time. Requests #2, #3, and #4 can be submitted at a separate time so as not to delay our receipt of #1.

If you have any questions please contact me.

Thank you,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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/s/

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Gregory F DiBernardo

8/7/2008 02:41:47 PM

CSO

NDA 22-26 Facsimile Transmission Clinical Request for Information

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising and Communication (DDMAC) Attention: Samuel Skariah, CSO**

FROM (Name, Office/Division, and Phone Number of Requestor): **Gregory DiBernardo, PM/ Joette Meyer, Acting Clinical Team Leader, DSPTP/(301) 796-4063**

DATE  
**August 7, 2008**

IND NO.

NDA NO.  
**22-268**

TYPE OF DOCUMENT  
**Package Insert, Carton and Container Labels**

DATE OF DOCUMENT  
**June 27, 2008**

NAME OF DRUG  
**Coartem (proposed)  
(artemether/lumefantrine)**

PRIORITY CONSIDERATION  
**Priority**

CLASSIFICATION OF DRUG  
**Antimalarial (4050120)**

DESIRED COMPLETION DATE  
**October 3, 2008**

NAME OF FIRM: **Novartis Pharmaceuticals Corporation**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** We are requesting a consult review for the carton and container labels and the package insert for Coartem (proposed trade name). Please note, the applicant did not agree with the recommendations from the 4/15/08 proprietary name review completed under PIND 75,287 and appealed the recommendations made by DMEPA. Therefore, the name Coartem listed on the package insert, carton, and container labels may change as this NDA progresses through the review cycle. The EDR link for the labeling information can be found at \\FDSWA150\NONECTD\N22268\N\_000\2008-06-27

Please note that the Annotated Label can be found in the Summary Folder (it is not in the Labeling Folder).

Coartem is an NME and a combination antimalarial drug (artemether and lumefantrine, also known as benflumetol) being developed for the treatment of acute, uncomplicated malaria in adults and children due to *P. falciparum*. The application has been granted a Priority review (PDUFA goal date of December 27, 2008). Also, since this is an NME, it will be discussed at an Advisory Committee meeting (per FDAAA) scheduled for December 3, 2008.

SIGNATURE OF REQUESTOR

Gregory DiBernardo

METHOD OF DELIVERY (Check one)

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/s/

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Gregory F DiBernardo  
8/7/2008 02:11:36 PM  
NDA 22-268 DDMAC Consult Request



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 7, 2008

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
Email: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem-Clinical Pharmacology request for information

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**Total no. of pages including cover:** 4

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**Comments:**

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Dear Ms. Kummerer,

In order to assist in the review of NDA 22-268, please address the following request for information from our Clinical Pharmacology team. Please note this request for information was originally communicated via an Email on August 1, 2008 (see attachment).

Your response to our request should be submitted as an official amendment to the NDA.

In the ‘*Summary of Biopharmaceutic Studies and Associated Analytical Methods and Summary of Clinical Pharmacology Studies*’ document, under section 5.3, *Exposure-response relationships*, you have indicated that the population PK and therapeutic response modeling of co-artemether have been evaluated in malaria patients (Ezzet, et al 1998 and Ezzet et al 2000) based on two studies conducted in Thailand (CCOA56A012 and CCOA566A025). We could not locate the full study report for the exposure-response (E-R) analysis and under the PK portion of the Study report CCOA566A025 we could not locate any E-R analysis. We request that you help us locate the study report for the E-R analyses.

If this material has been previously submitted, provide the date of submission and clear instructions on how to locate the requested material in that submission.

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Email Sent on August 1, 2008:**

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**From:** DiBernardo, Gregory  
**Sent:** Friday, August 01, 2008 11:53 AM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** Chilukuri, Dakshina; Colangelo, Philip M; Willard, Diana M  
**Subject:** NDA 22-268-Coartem-Novartis-Request for Study Report (E-R) analysis

Hello Susan,

This email is being sent at this time informally, but an official facsimile will follow shortly. You can respond to this email, by providing your comments as a desk copy electronically, but please remember to submit the official submission to the Electronic Document Room for this NDA.

Our Clinical Pharmacology reviewer has identified the following concern:

In the *'Summary of Biopharmaceutic Studies and Associated Analytical Methods and Summary of Clinical Pharmacology Studies'* document, under section 5.3, *Exposure-response relationships*, you have indicated that the population PK and therapeutic response modeling of co-artemether have been evaluated in malaria patients (Ezzet, et al 1998 and Ezzet et al 2000) based on two studies conducted in Thailand (CCOA56A012 and CCOA566A025). We could not locate the full study report for the exposure-response (E-R) analysis and under the PK portion of the Study report CCOA566A025 we could not locate any E-R analysis. We request that you help us locate the study report for the E-R analyses.

Susan if this material has been previously submitted please provide the date it was submitted and clear directions on how to locate the requested material in that submission. If this material has not been submitted, please go ahead and submit this material to the NDA.

Thank you,

**Gregory F. DiBernardo**  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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/s/

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Gregory F DiBernardo

8/7/2008 02:35:40 PM

CSO

NDA 22-268 Facsimile Transmission Clinical Pharmacology request for study  
report exposure-response (E-R) analysis



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODEIV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 29, 2008

<b>To:</b> James L. DeMartino, Ph.D.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-2565	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-2645	<b>Phone number:</b> 301-796-1600
Email: james.demartino@novartis.com	

**Subject:** NDA 22-268-Coartem-request for additional Clinical information for NDA Review

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**Total no. of pages including cover:** 3

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**Comments:**

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**Document to be mailed:**  YES  NO

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Dear Dr. DeMartino,

Regarding your NDA 22-268, our Clinical review team would like to request further clarification on the following information. If any of this information has been previously submitted, provide the date of submission and the location of the material within that submission.

- Please provide a summary of the existing worldwide post-marketing safety data available for Coartem/Riamet.
- Please provide the location of the Coding Dictionary used for all studies
- Please make available the subject Case Report Forms for all subjects who died and/or had Serious Adverse Events for the following 6 dose Coartem studies: Studies 030, ABD01, and ABR01.
- Please explain why the same subject number (00203) has been used for two different subjects in Study B2303.  
B2303 (b) (4) /0301/00203 and B2303 (b) (4) /0601/00203
- As requested at the Pre-NDA meeting, please submit a discussion of the efficacy of Coartem in immune compared to non-immune patients and as part of your discussion please provide your rationale for assuming the applicability of foreign data to the U.S. population.

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo  
7/29/2008 09:24:31 AM  
CSO

NDA 22-268 Facsimile Transmission Clinical Information Request

# DSI CONSULT: Request for Clinical Inspections

**Date:** 07/17/2008

**To:** Tejashri Purohit-Sheth, M.D., in HFD-47, Good Clinical Practice Branch  
(GCP)-2, DSI, Office of Compliance  
Susan Thompson, DSI Primary Reviewer

**Through:** Renata Albrecht, M.D./Director/ Division of Special Pathogen and Transplant  
Products (DSPTP)  
Joette Meyer, Pharm.D./Acting Team Leader/DSPTP  
Elizabeth O'Shaughnessy, M.D./Medical Reviewer/DSPTP

**From:** Gregory DiBernardo/Regulatory Health Project Manager/DSPTP

**Subject:** Request for Clinical Site Inspections

## **I. General Information**

Application#: NDA 22-268  
Novartis Pharmaceuticals Corporation  
One Health Plaza  
Bldg 405/4051  
East Hanover, NJ 07936-1080  
James DeMartino, Ph.D.  
Director, Drug Regulatory Affairs  
(862) 778-2645  
james.demartino@novartis.com

Drug: Coartem (artemether/lumefantrine) Tablet

NME: Yes

Standard or Priority: To Be Determined

Study Population < 18 years of age: Yes (both adult and pediatric subjects were studied)

Pediatric exclusivity: There are no studies in NDA 22-268 that were conducted to obtain six months pediatric exclusivity.

PDUFA: To Be Determined

Action Goal Date: To Be Determined

Inspection Summary Goal Date: To Be Determined

**Note: This NDA was received on June 27, 2008. A determination if this will be a priority or standard review will be made at the July 28, 2008 Filing Meeting.**

## II. Background Information

*Include a brief introduction about the application and include the following:*

- *New application:* Yes
- *Proposed indication:* Treatment of malaria in patients of 5kg body weight and above with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*.

### *Brief information*

*On drug:* Increasing resistance to conventional antimalarial drugs in *P. falciparum* has led to a pressing need for the development of new drugs for the treatment of malaria. Combination antimalarial treatment is central not only to the successful treatment of individual patients but also for public health control of malaria. Artemether/lumefantrine (Coartem) was the first fixed dose combination of an artemisinin derivative with a second unrelated antimalarial compound. Lumefantrine (formerly benflumetol) is an aryl amino alcohol in the same general group as mefloquine and halofantrine. Each tablet consists of 20 mg artemether and 120 mg lumefantrine. The rationale for this combination is that artemether rapidly reduces parasitemia and the long-acting lumefantrine eliminates residual parasites. A three-day treatment schedule with a total of six doses is recommended (see attached proposed label). Coartem has shown efficacy in the treatment of uncomplicated malaria in adults and in children. The most common adverse drug reactions associated with Coartem include CNS reactions (headache, dizziness) and gastrointestinal reactions (abdominal pain, anorexia). Other common side effects include CNS (sleep disorders), gastrointestinal (diarrhea, vomiting, nausea), CVS (palpitations), dermatologic (pruritis, rash), respiratory (cough), and musculo-skeletal adverse reactions (arthralgia, myalgia).

- *Disease:* Malaria is a life-threatening infection that occurs in many tropical and subtropical regions of the world. Approximately, 40% (2.5 billion people) of the world's population, mostly those living in developing countries, are at risk of malaria. More than 500 million people become severely ill with malaria every year and more than 1 million die from the effects of the disease. Malaria in humans is caused by intra-erythrocytic protozoa of the genus *Plasmodium* (i.e., *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* and *P. knowlesi*). Malaria is transmitted by the female *Anopheles* mosquitoes. *P. falciparum* causes the most severe form of malaria and is associated with a high morbidity and mortality. Chloroquine-resistant *P. falciparum* malaria is widespread in Africa and Asia. There are also recent reports of chloroquine resistance in *P. vivax*. Travelers to sub-Saharan Africa have the greatest risk of both getting malaria and dying from their infection. However, all travelers to endemic countries are at risk. The majority of malaria infections in the United States occur among persons who have traveled to areas with ongoing malaria transmission. In the United States, cases can also occur through exposure to infected blood products, congenital transmission, or local mosquito-borne transmission. The CDC received reports of 1,564 cases of malaria in the United States in 2006, six of which were fatal. *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* were identified in 39.2%, 17.6%, 2.9%, and 3.0% of cases, respectively. Ten patients (0.6%) were infected by two or more species. Overall, the numbers of malaria cases has remained relatively stable from 2001 to 2006. Based on estimated volume of travel, the highest estimated relative case rates of malaria among travelers occurred among those returning from West Africa.

- *Pivotal studies (to include brief summary of protocols, pertinent endpoints, and concerns with application):* Eight key studies (023, ABMO2, 025, 026, 028, 2401, 2403, 2303) have been identified in the NDA 22-268. Please see **Attachment 1, pages 3 through 16**, for a tabular listing of these studies (prepared by the applicant) with a brief summary of the protocols and pertinent endpoints. The primary endpoint for these studies is the 28-day cure rate. The primary efficacy variables were defined as:

- 28 day cure rate, which is the proportion of patients with clearance of asexual parasitemia within 7 days of initiation of trial treatment, without subsequent recrudescence.
- Time to parasite clearance (PCT) = time from first dose until first total and continued disappearance of asexual parasite forms which remains for at least a further 48 hours.
- Time to fever clearance (FCT) = time from first dose until the first time body temperature falls below 37.5°C and remains below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline).

There are no major concerns regarding the efficacy or safety of the Coartem based on the data reviewed thus far in the NDA.

### III. Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Beijing, China: Site 01 Jiao Xiu-Qing, M.D (Retired) Institute of Microbiology and Epidemiology, AMMS, Beijing, China	# A023 # ABMO2	A023: n = 153; ABMO2: n = 157	Uncomplicated <i>P. falciparum</i> malaria and mixed infection with <i>P. falciparum</i>
Bangkok, Thailand: Site 01 Hospital for Tropical Diseases Faculty of Tropical Medicine Mahidol University Bangkok, Thailand	#025 #026 #028	#025: n = 100 #026: n = 28 #028: n = 219	Uncomplicated <i>P.</i> <i>falciparum</i> malaria and mixed infection with <i>P. falciparum</i>
Dr. Francois Nosten MaeLa Camp Shoklo Malaria Research Unit Mae Sot, Thailand	#025 Site 03 And #026 Site 02	#025: n=259 #026: n=172	

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Kilifi, Kenya: Site 01 Dr. Michael Makanga Kenya Medical Research Institute, KEMRI Kilifi, Kenya	#2403	n =107	Uncomplicated <i>P. falciparum</i> malaria and mixed infection with <i>P.falciparum</i> in infants (≥ 5 kg) and children
<b>OR</b>			
Ibadan, Nigeria : Site 02 Dr. Catherine Falade University College Hospital Malaria Research Laboratories, Institute for Advance Medical Research and Training. Ibadan, Nigeria	#2403	N=10	Uncomplicated <i>P.</i> <i>falciparum</i> malaria and mixed infection with <i>P.falciparum</i> in infants (≥ 5 kg) and children
<b>OR</b>			
Dar es salam, Tanzania: Site 03 Prof. Zul Premji Muhimbili University College of Health Sciences Department of Parasitology and Medical Entomology Dar es salam, Tanzania	#2403	N=100	Uncomplicated <i>P.</i> <i>falciparum</i> malaria and mixed infection with <i>P.falciparum</i> in infants (≥ 5 kg) and children
<b>OR</b>			
Dar es Salaam, Tanzania: Site 301 Salim Abdulla, Dr. Ifakara Health Research and Development Centre Dar es salaam, Tanzania	#2303	n = 240	Uncomplicated <i>P.</i> <i>falciparum</i> malaria and mixed infection with <i>P.falciparum</i> in infants (≥ 5 kg) and children

#### **IV. Site Selection/Rationale**

*Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.*

A DSI consult was requested because Coartem is a new molecular entity for the treatment of malaria. There are no major concerns regarding the efficacy or safety of the drug based on the data provided in the current NDA. The NDA studies were not conducted under IND. It does not appear that any one site is driving efficacy. The sites of Dr. Xiu-Qing (China), the Hospital for Tropical Diseases in Thailand and Dr. Nosten's site, also in Thailand, and one additional site in Africa (Kenya, Tanzania, or Nigeria) that enrolled infants and children are the sites of greatest interest.

Two of the key studies that are pivotal to the approval of Coartem were performed at Site 01 in China. These two studies compared Coartem to its individual components, artemether and benflumetol (subsequently known as lumefantrine).

Site 01 in Thailand was common to Study 025, 26 and 28. Dr. Nosten site in Thailand also participated in multiple studies (025 and 026). We would like to focus on study 25 for two reasons: 1) in this study, the applicant compared the four-dose regimen and the six-dose regimen of Coartem and 2) it was conducted in an area of chloroquine-resistant *P. falciparum* malaria.

The applicant requests an indication for the treatment of malaria in children. There are large numbers of small children ( $\geq 5$ kg weight and upward) in the studies conducted in Tanzania, Kenya and Nigeria, therefore at least one of these sites should be included.

### ***Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results? We are still evaluating the studies.*

However, at this time it does not appear that any particular site is driving the results.

Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites? From what has been reviewed to date, there seems to be consistency in efficacy among the various studies. However, since this is a combination product, it will be very important for us to assess the added benefit of each product to the combination. Only two studies (A23 and ABM02) assess this added benefit. Both of these studies are single center studies and both were conducted at the Beijing, China Site 01 by Jiao Xiu-Qing, M.D., Institute of Microbiology and Epidemiology, AMMS, Beijing, China, listed above.

- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites? To be determined.*
- *Are there concerns that the data may be fraudulent or inconsistent? Not at this time.*
  - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct? We are still evaluating the studies. We do not suspect trial misconduct at this time.*
- *Is this a new molecular entity? Yes*
- *Is the data gathered solely from foreign sites? Yes*
- *Were the NDA studies conducted under an IND? No*

### ***Rationale for DSI Audits***

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**Five or More Inspection Sites (delete this if it does not apply):**

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

We are requesting three sites be inspected. Site 01 in China, Site 01 in Thailand, Dr. Nosten's site in Thailand (Site 03 in Study 025 and Site 02 in Study 026) and one site in Africa (Kenya, Nigeria, or Tanzania). Please see section IV above for rationale.

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**V. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

**Data to be verified in adults and children.**

- **Parasite Counts**
  - Do the asexual parasite counts at baseline match original laboratory data from malaria smears?
  - Did blood asexual parasite counts decline to zero on the day stated in CRF?
  - Were recurrences of asexual parasitemia up to 28 days reported accurately?
- **Adverse Events**

Did the sites capture neurologic, hepatic, and cardiac adverse events (related to prolonged QT interval) accurately?

- **Withdrawal from study:** Did any patient withdraw from a study due to undocumented adverse events?
- **Additional anti-Malaria Drugs**  
Were additional antimalarial drugs used during the studies that were not recorded as rescue therapy?
- **Severe Malaria**  
Did any patient develop severe malaria during the study period and was this documented accurately?

Should you require any additional information, please contact Gregory DiBernardo at the following telephone number: 301-796-4063. Alternatively, you may contact Elizabeth O'Shaughnessy at 301-796-0781.

Concurrence: (as needed)

\_\_\_\_\_ Medical Team Leader  
\_\_\_\_\_ Medical Reviewer  
\_\_\_\_\_ Director, Division Director (for foreign inspection requests  
only)

47 Page(s) Withheld

       Trade Secret / Confidential

X Draft Labeling

       Deliberative Process

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/s/

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Renata Albrecht  
7/17/2008 10:30:25 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): QT-IRT  
Attention: Mr. Devi Kozeli, CSO, DCRP

FROM (Name, Office/Division, and Phone Number of Requestor):  
Gregory DiBernardo, PM/ Joette Meyer, Acting CRTL,  
DSPTP/(301) 796-4063

DATE  
July 17, 2008

IND NO.

NDA NO.  
22-268

TYPE OF DOCUMENT  
QT study report,  
Sequence # 017

DATE OF DOCUMENT  
June 02, 2008

NAME OF DRUG  
Coartem  
(artemether/lumefantrine)

PRIORITY CONSIDERATION  
To be determined

CLASSIFICATION OF DRUG  
Antimalarial (4050120)

DESIRED COMPLETION DATE  
September 15, 2008

NAME OF FIRM: Novartis Pharmaceuticals Corporation

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Coartem is a NME and a combination antimalarial drug (artemether and lumefantrine, also known as benflumetol) being developed for the treatment of acute, uncomplicated malaria in adults and children due to *P. falciparum*. The applicant has requested a Priority review, which means a PDUFA goal date of December 27, 2008, if Priority designation is granted. Also, since this is an NME it will be discussed at an Advisory Committee meeting tentatively scheduled for November 2008.

Lumefantrine is chemically related to another antimalarial, halofantrine. Halofantrine is known to be associated with significant prolongation of the QTc interval. In addition, measurement of the QT interval during a malarial episode and recovery can be complicated by the fact that the disease affects cardiac electrophysiology, including a lengthening of the QT interval (due to anemia) and an increased heart rate (which can be overcorrected with some QT correction formulae).

Therefore, the applicant has conducted a "thorough QT" study in healthy adults: Study CCOA566A2101: "A randomized, single-blind, parallel group, multiple-dose study to evaluate the effects of the oral 6-dose regimen of

COA566 on cardiac safety in healthy subjects versus placebo with positive control (moxifloxacin hydrochloride)".

In addition, the applicant has also conducted two other studies evaluating the QT effect of artemether/lumefantrine on healthy adult volunteers: Study CCOA566A1022: "Open Pilot study to evaluate cardiac effects and plasma concentrations of the antimalarials co-artemether (artemether and benflumetol) and halofantrine in healthy male subjects after single oral doses taken with food", and Study CCOA566A024: "Comparison of cardiac effects of the antimalarials co-artemether and halofantrine in relation of the plasma concentrations of the study drugs in healthy male volunteers after single oral doses taken with a high fat meal."

Reports for Studies 2101, 1022, and 024 are contained in NDA 22-268, sequence number 017 dated June 02, 2008. The EDR link for these study reports is: \\FDSWA150\NONECTD\N22268\R\_010\2008-06-02

ECG evaluations were also performed in most of the NDA clinical trials in adults and children with malaria. The method of ECG reading varied between the studies - some were read only by investigators, some were also peer reviewed by an independent cardiologist, and some were analyzed independently by a specialist CRO. The applicant has provided QT outlier analyses for these studies. The clinical QTc outlier analyses can be found in the EDR submission, NDA 22-268 dated July 2, 2008.

The EDR link for QTc outlier data is: \\FDSWA150\NONECTD\N22268\N\_000\2008-07-02.

A summary can also be found in the Clinical Overview, Section 5.4.2

\\FDSWA150\NONECTD\N22268\N\_000\2008-06-27

Of note, two of the studies, Study 5669701023 and ABMO2, in the NDA were factorial design studies in which Coartem was compared to each of the individual components. These studies may be of use to examine the QT effects of artemether and lumefantrine separately. The EDR links are:

Study ABMO2: \\FdsWA150\nonectd\N22268\R\_019\2008-06-05

Study 023: \\FDSWA150\NONECTD\N22268\R\_007\2008-04-08

The applicant also evaluated all AEs potentially related to QT interval prolongation: see Clinical Overview Section 5.2.5 \\FDSWA150\NONECTD\N22268\N\_000\2008-06-27

Additional supporting documentation requested by the QT-IRT for this consult can be found in the EDR, NDA 22-268 dated July 9, 2008. The EDR link for supporting documentation is:

\\FDSWA150\NONECTD\N22268\N\_000\2008-07-09

Questions for the QT-IRT:

Please comment on whether or not the TQT study was conducted appropriately and on the clinical significance of the QT prolongation in adults and children seen in the healthy volunteer studies and in the malaria clinical trials. Also, please recommend appropriate labeling for the QT prolonging potential of artemether/lumefantrine.

Applicant's Proposed Annotated label:

\\FDSWA150\NONECTD\N22268\N\_000\2008-06-27

Please forward any comments that you have for this QT-IRT Consult to the DSPTP. Thank you for your help.

SIGNATURE OF REQUESTOR

Gregory DiBernardo

METHOD OF DELIVERY (Check one)

DFS

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MAIL

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/s/

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Gregory F DiBernardo  
7/17/2008 12:56:39 PM  
NDA 22-268 IRT Consult Request for QT Study Reports



NDA 22-268

**NDA ACKNOWLEDGMENT**

Novartis Pharmaceuticals Corporation  
Attention: James L. DeMartino, Ph.D.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Dr. DeMartino:

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

Name of Drug Product: Coartem, (artemether 20mg/lumefantrine 120mg) Tablet

Date of Application: June 27, 2008

Date of Receipt: June 27, 2008

Our Reference Number: NDA 22-268

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 26, 2008, in accordance with 21 CFR 314.101(a).

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.

Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Mr. Gregory F. DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Judit Milstein  
Chief, Project Management Staff  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Judith Milstein  
7/11/2008 05:13:00 PM  
NDA 22-268 Acknowledgment Letter



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODEIV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 9, 2008

<b>To:</b> James L. DeMartino, Ph.D.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-2565	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-2645	<b>Phone number:</b> 301-796-1600
Email: james.demartino@novartis.com	

**Subject:** NDA 22-268-Coartem-Microbiology request for information

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**Total no. of pages including cover:** 4

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**Comments:**

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**Document to be mailed:**             YES                     NO

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Dear Dr. DeMartino,

Please see the following request for information from our Microbiology team in support of NDA 22-268.

1. The references provided in support of the PCR assay were for the purpose of epidemiological studies (Felger et al., 2002, *Meth. Mol. Med.*, 72:117). However, its use in clinical trials for distinguishing new infection from recrudescence has not been validated. The following information should be submitted for our review:
  - a. Please clarify whether the PCRs used in the studies which are cited in the labeling utilized the same technique across studies and study sites and if the assays were performed in the same laboratory.
  - b. Please submit the methodology and performance characteristics of the assays which include the ability of the assay to distinguish infections with a single clone/strain from infections with mixed strains/clones.
  - c. The data supporting the lower limit of detection of the assay need to be submitted.
  - d. The actual gel results which will allow us to distinguish patients with new infections from those who were determined to be recrudescence infections needs to be submitted. Please note the following scenario and provide comment. Scenario: A patient enters the trial with a mixed infection of strains A and B. Strain B is present below the lower limit of detection of the assay such that only strain A is seen upon PCR genotyping. Following drug treatment, the therapy was successful in eliminating strain A, but not strain B. Upon follow-up PCR genotyping, it was found that strain B was detectable as the infecting pathogen. How could this situation be determined to be a treatment failure and not classified as a new infection with strain B?
  - e. Please provide details on the number of different strains which were detected at the study sites which utilized PCR. Moreover, please describe any controls which were used that allowed the positive identification of a specific strain or the detection of a mixed infection.
  - f. In EFF dataset of study ABMO2 there are two columns listed: PCR\_1C and PCR\_1A for which there is a code (the number "66") in PCR\_1C and the word "missing" in the PCR\_1A column. The number "66" and "missing" only appear in rows corresponding to patients who were observed to have reappearance of parasites. Please clarify the meaning of these data columns as the use of PCR to distinguish between recrudescence and a new infection was not specified in the study. Also, it is unclear whether the method used was the same as the method used in other studies.
2. Thank you for providing annotation to the labeling, however, it seems that not all claims within the microbiology sections (sections 12.1 and 12.2) are linked to study reports. For example, in Section 12.2 it is stated that "strains of *P. falciparum* with a moderate decrease in susceptibility to artemether or lumefantrine alone can be selected *in vitro* or *in vivo*", however there are no links to the reports which define these phenomena both *in vitro* and *in vivo*. A more detailed annotation should be submitted to aid our review.

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo

7/9/2008 04:56:01 PM

CSO

NDA 22-268 Facsimile Transmission Request for Microbiology Information



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODEIV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 2, 2008

<b>To:</b> James L. DeMartino, Ph.D.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Health Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> 973-781-3966	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-2645	<b>Phone number:</b> 301-796-1600
Email: james.demartino@novartis.com	

**Subject:** NDA 22-268-Coartem-request for further clarification on formulation of Coartem used in 8 key studies and supportive studies.

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:**             YES                     NO

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Dear Dr. DeMartino,

Regarding NDA 22-268, which includes the submissions of the 8 key clinical studies and the supportive studies using 6-dose and 4-dose regimens of Coartem, please address the following request:

Please submit information detailing the formulation of Coartem used in each of the eight key clinical studies as well as in the supportive studies using the 6-dose and 4-dose regimens.

Explain how the formulation used in the clinical studies differs from the to-be-marketed formulation of Coartem.

If this information has already been provided to the Agency in your NDA submission, please provide directions on where to locate it.

If you have any questions regarding this facsimile transmission, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Health Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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Gregory F DiBernardo

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CSO

NDA 22-268 Facsimile Transmission Request for Further Clarification on  
Formulation of Coartem used in 8 Key Clinical  
and Supportive Studies



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on December 17, 2008. The purpose of the teleconference was to inform Novartis of some recent concerns regarding FDA Office of Compliance manufacturing facilities inspections.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** December 17, 2008

**APPLICATION NUMBER:** NDA 22-268

**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

### Novartis Pharmaceuticals Corporation

Susan Kummerer, M.S.

Paula Rinaldi

John Orloff, M.D.

Mike Bruckheimer

Vivianne Arencibia

Anne-Claire Marrast, M.D.

(b) (4)

Heiner Grueninger, Ph.D.

Verena Walters

Fanny Ki, Ph.D.

Daniel Stein

Director, Drug Regulatory Affairs

Director, Drug Regulatory Affairs

Head U.S. Medical and Drug Regulatory Affairs

FDA Compliance Liaison, Novartis Group Quality Operations

Vice President Group Compliance Services, Novartis Group Quality Operations

Global Program Medical Director

Global Program Head, Trop Med Initiatives & EGM Statistics

Group Head Biostatistics

Pharmacokinetics

**AND:**

### Food and Drug Administration

Edward Cox, M.D.

Renata Albrecht, M.D.

Anthony Charity

Carmello Rosa

Elizabeth Johnson

Norman Schmuff, Ph.D.

Rapti Madurawe, Ph.D.

Joette Meyer, Pharm. D.

Elizabeth O'Shaughnessy, M.D.

Sue Lim, M.D.

Ozlem Belen, M.D.

Philip Colangelo, Pharm.D., Ph.D.

Dakshina Chilukuri, Ph.D.

William Taylor, Ph.D.

Owen McMaster, Ph.D.

Terry Miller, Ph.D.

Director, Office of Antimicrobial Products

Director, Division of Special Pathogen and Transplant Products, (DSPTP)

Office of Compliance, Division of Manufacturing and Product Quality, (DMPQ), Compliance Officer

Office of Compliance, DMPQ, Acting Team Leader, Compliance Officer

Office of Compliance, DMPQ, Consumer Safety Officer  
Branch Chief, Office of New Drug Quality Assessment, (ONDQA)

Pharmaceutical Assessment Lead, ONDQA

Acting Clinical Team Leader, DSPTP

Clinical Reviewer-Efficacy, DSPTP

Clinical Reviewer-Safety, DSPTP

Clinical Reviewer-Pediatric Safety, DSPTP

Clinical Pharmacology Team Leader, DSPTP

Clinical Pharmacology Reviewer, DSPTP

Pharmacology/Toxicology Team Leader, DSPTP

Pharmacology/Toxicology Reviewer, DSPTP

Pharmacology/Toxicology Reviewer, DSPTP

Shukal Bala, Ph.D.	Microbiology Team Leader, DSPTP
Aaron Ruhland, Ph.D.	Microbiology Reviewer, DSPTP
Simone Shurland, Ph.D.	Microbiology Reviewer, DSPTP
Xianbin Li, Ph.D.	Biostatistics Reviewer, DSPTP
Lan Zeng, M.A.	Biostatistics Reviewer, DSPTP
Patrick Archdeacon, M.D.	Clinical Reviewer, DSPTP
Diana Willard	Chief, Project Management Staff, DSPTP
Gregory DiBernardo	Regulatory Project Manager, DSPTP

**SUBJECT:** Briefly discuss concerns regarding foreign manufacturing facilities inspections for this NDA.

**BACKGROUND:**

This teleconference was originally arranged to continue on-going labeling discussions between Division of Special Pathogen and Transplant Products (DSPTP) and Novartis Pharmaceuticals Corporation (Novartis). However, the FDA Project Manager, Mr. DiBernardo, telephoned Novartis on December 16, 2008, to state that the FDA Office of Compliance (OC) had concerns regarding some of the foreign manufacturing facilities inspections. He stated that a brief and general outline of these concerns would be provided to Novartis at the beginning of the labeling teleconference scheduled for the morning of December 17, 2008 and that a second teleconference scheduled by the FDA Office of Compliance would be made for later in the day on December 17, 2008. At the second teleconference, specific questions and concerns could be addressed by the FDA Office of Compliance staff and the Office of New Drug Quality Assessment (ONDQA) staff.

**SUMMARY:**

Following introductions, Dr. Cox stated that due to deficiencies noted at several foreign manufacturing facilities included in the NDA, specifically the (b) (4) facility in China, the Novartis testing facility in Basel, Switzerland, and the (b) (4) facility in Switzerland, DSPTP would not take an action on or before the PDUFA Goal Date of December 27, 2008. Dr. Cox stated that the PDUFA Goal Date would not be extended, instead it would be missed. He further stated that FDA would need more time to complete the review of the materials requested by the Office of Compliance in order to address the deficiencies noted at these sites. Dr. Cox emphasized that the review team will continue to work on the product labeling with Novartis as well as all other aspects of the NDA review.

Anthony Charity from FDA's Office of Compliance had requested that Novartis confirm/clarify the addresses of the (b) (4). The address for (b) (4) in the application was different than the address reported in a 2007 inspection for another product. Novartis agreed to provide information related to the correct address at the teleconference that would occur later in the day.

After Dr. Cox and Mr. Charity made their remarks regarding the foreign manufacturing facilities, these individuals left the teleconference and the scheduled labeling teleconference began and progressed with the remaining personnel from DSPTP and Novartis. Staff from the Office of Compliance organized and provided Novartis staff the necessary information for the teleconference which occurred later in the day.

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Gregory DiBernardo  
Regulatory Project Manager

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/s/

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Joette Meyer

4/6/2009 12:35:40 PM



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on December 22, 2008. The purpose of the teleconference was to follow up on a previous teleconference and to clarify the outstanding concerns related to FDA Office of Compliance manufacturing facilities inspections.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** December 22, 2008

**APPLICATION NUMBER:** NDA 22-268

**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

**Novartis Pharmaceuticals Corporation**

John Orloff, M.D.	Head U.S. Medical and Drug Regulatory Affairs
Paula Rinaldi	U.S. Mature Products, Drug Regulatory Affairs
Susan Kummerer, M.S.	Director, Drug Regulatory Affairs
Joan Materna	Manager, Drug Regulatory Affairs (CMC)
Vivianne Arencibia	Vice President Group Compliance Services, Novartis Group Quality Operations
Mike Bruckheimer	Corporate Compliance Officer, Global Quality Operations

**AND:**

**Food and Drug Administration**

Edward Cox, M.D.	Director, Office of Antimicrobial Products
Renata Albrecht, M.D.	Director, Division of Special Pathogen and Transplant Products, (DSPTP)
David Roeder	Associate Director for Regulatory Affairs, Office of Antimicrobial Products
Anthony Charity	Office of Compliance, Division of Manufacturing and Product Quality, (DMPQ) Compliance Officer
Kennerly Chapman	Office of Compliance, DMPQ, Project Management Officer
Elizabeth Johnson	Office of Compliance, DMPQ, Consumer Safety Officer
Norman Schmuff, Ph.D.	Branch Chief, Office of New Drug Quality Assessment, (ONDQA)
Rapti Madurawe, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Joette Meyer, Pharm. D.	Acting Clinical Team Leader, DSPTP
Diana Willard	Chief, Project Management Staff, DSPTP
Gregory DiBernardo	Regulatory Project Manager, DSPTP

**SUBJECT:** Follow up to discuss concerns regarding foreign manufacturing facilities inspections

**BACKGROUND:**

Novartis Pharmaceuticals Corporation (Novartis) was informed at the beginning of a scheduled labeling teleconference with Division of Special Pathogen and Transplant Products (DSPTP) on December 17, 2008 of concerns regarding FDA Office of Compliance inspections at a number of their foreign manufacturing facilities. A second teleconference was held later that day with Novartis, FDA Office of Compliance/ Division of Manufacturing and Product Quality (DMPQ); Office of New Drug Quality Assessment (ONDQA); Office of Antimicrobial Products (OAP), and DSPTP to discuss these concerns with Novartis. After the second teleconference on December 17, 2008, DSPTP contacted Novartis to

arrange another teleconference on December 22, 2009 to clarify with Novartis Compliance Services the steps to be taken to resolve the outstanding inspection issues.

### **SUMMARY:**

DMPQ outlined the following outstanding manufacturing facility inspection issues for this NDA:

1. (b) (4) a complete analysis of an unknown impurity peak in a column at this facility needs to be submitted to and reviewed by the FDA prior to an action being taken.
2. (b) (4): as there was confusion regarding the exact address for one of the Chinese manufacturing facilities, the FDA plans to re-inspect this facility. (b) (4) facilities are scheduled for inspection in early 2009. These (b) (4) facilities can only be utilized under the NDA after the FDA inspection is complete and the facilities are found to be in compliance.

It was emphasized that the FDA will need to conduct the scheduled inspections of the (b) (4) and (b) (4) facilities in China and that Novartis will need to resolve all outstanding issues from the (b) (4) facility prior to the Agency moving forward with an action. Novartis raised the possibility of withdrawing from the NDA the (b) (4) facilities in China that have not yet been inspected, thus relying on the other facilities to support this application. Dr. Cox responded that withdrawing these two sites would be a business decision made by Novartis. ONDQA noted that the (b) (4) facility is needed for the NDA as it is the major supplier for artemether.

Novartis raised the question that if the data for (b) (4) is submitted prior to December 23, 2008, would FDA still require (b) (4) to be inspected. Anthony Charity from DMPQ stated that FDA would still need to inspect the (b) (4) to verify what address is used for manufacturing of the API stated in the application and that there is a possibility due to the holidays that the evaluation would not be completed in a timely matter that would satisfy a recommendation by December 23, 2008.

Novartis acknowledged the inspection issues at the (b) (4) facility will need to be addressed satisfactorily before the Agency can take an approval action. Novartis stated that the results from the column with the unknown impurity peak will not be available until "after the holidays." This column is being shipped from China to Basel, Switzerland and is currently in transit. However, there are some data available from another column that is similar to the column with the unknown peak and these results could be submitted as early as December 23, 2008.

Dr. Cox stated that even if DSPTP does not take an action by the PDUFA goal date, the Division will continue to work with Novartis to resolve all outstanding issues. In response to a question from Novartis regarding whether it would be possible to request priority inspections of the (b) (4) facilities, DMPQ indicated that the Chinese inspections are currently scheduled to occur in February 2009 and since they are already "on the books" it would not be possible to conduct the inspection any sooner.

### **Addendum to the Meeting:**

DMPQ spoke with Novartis later in the day on December 22, 2008 and informed them that the FDA will not be able to meet the December 27, 2008 PDUFA date. The results from the original column from (b) (4) must be submitted and found satisfactory prior to approval and as Novartis had indicated that these data would not be available until after December 27, 2008, the PDUFA goal date will be missed.

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Gregory DiBernardo  
Regulatory Project Manager

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/s/

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Joette Meyer

4/6/2009 12:35:58 PM



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on December 17, 2008. The purpose of the teleconference was to inform Novartis of some recent concerns regarding FDA Office of Compliance manufacturing facilities inspections.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** December 17, 2008

**APPLICATION NUMBER:** NDA 22-268

**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

### Novartis Pharmaceuticals Corporation

Susan Kummerer, M.S.

Paula Rinaldi

John Orloff, M.D.

Mike Bruckheimer

Vivianne Arencibia

Anne-Claire Marrast, M.D.

(b) (4)

Heiner Grueninger, Ph.D.

Verena Walters

Fanny Ki, Ph.D.

Daniel Stein

Director, Drug Regulatory Affairs

Director, Drug Regulatory Affairs

Head U.S. Medical and Drug Regulatory Affairs

FDA Compliance Liaison, Novartis Group Quality Operations

Vice President Group Compliance Services, Novartis Group Quality Operations

Global Program Medical Director

Global Program Head, Trop Med Initiatives & EGM Statistics

Group Head Biostatistics

Pharmacokinetics

**AND:**

### Food and Drug Administration

Edward Cox, M.D.

Renata Albrecht, M.D.

Anthony Charity

Carmello Rosa

Elizabeth Johnson

Norman Schmuff, Ph.D.

Rapti Madurawe, Ph.D.

Joette Meyer, Pharm. D.

Elizabeth O'Shaughnessy, M.D.

Sue Lim, M.D.

Ozlem Belen, M.D.

Philip Colangelo, Pharm.D., Ph.D.

Dakshina Chilukuri, Ph.D.

William Taylor, Ph.D.

Owen McMaster, Ph.D.

Terry Miller, Ph.D.

Director, Office of Antimicrobial Products

Director, Division of Special Pathogen and Transplant Products, (DSPTP)

Office of Compliance, Division of Manufacturing and Product Quality, (DMPQ), Compliance Officer

Office of Compliance, DMPQ, Acting Team Leader, Compliance Officer

Office of Compliance, DMPQ, Consumer Safety Officer  
Branch Chief, Office of New Drug Quality Assessment, (ONDQA)

Pharmaceutical Assessment Lead, ONDQA

Acting Clinical Team Leader, DSPTP

Clinical Reviewer-Efficacy, DSPTP

Clinical Reviewer-Safety, DSPTP

Clinical Reviewer-Pediatric Safety, DSPTP

Clinical Pharmacology Team Leader, DSPTP

Clinical Pharmacology Reviewer, DSPTP

Pharmacology/Toxicology Team Leader, DSPTP

Pharmacology/Toxicology Reviewer, DSPTP

Pharmacology/Toxicology Reviewer, DSPTP

Shukal Bala, Ph.D.	Microbiology Team Leader, DSPTP
Aaron Ruhland, Ph.D.	Microbiology Reviewer, DSPTP
Simone Shurland, Ph.D.	Microbiology Reviewer, DSPTP
Xianbin Li, Ph.D.	Biostatistics Reviewer, DSPTP
Lan Zeng, M.A.	Biostatistics Reviewer, DSPTP
Patrick Archdeacon, M.D.	Clinical Reviewer, DSPTP
Diana Willard	Chief, Project Management Staff, DSPTP
Gregory DiBernardo	Regulatory Project Manager, DSPTP

**SUBJECT:** Briefly discuss concerns regarding foreign manufacturing facilities inspections for this NDA.

**BACKGROUND:**

This teleconference was originally arranged to continue on-going labeling discussions between Division of Special Pathogen and Transplant Products (DSPTP) and Novartis Pharmaceuticals Corporation (Novartis). However, the FDA Project Manager, Mr. DiBernardo, telephoned Novartis on December 16, 2008, to state that the FDA Office of Compliance (OC) had concerns regarding some of the foreign manufacturing facilities inspections. He stated that a brief and general outline of these concerns would be provided to Novartis at the beginning of the labeling teleconference scheduled for the morning of December 17, 2008 and that a second teleconference scheduled by the FDA Office of Compliance would be made for later in the day on December 17, 2008. At the second teleconference, specific questions and concerns could be addressed by the FDA Office of Compliance staff and the Office of New Drug Quality Assessment (ONDQA) staff.

**SUMMARY:**

Following introductions, Dr. Cox stated that due to deficiencies noted at several foreign manufacturing facilities included in the NDA, specifically the (b) (4) facility in China, the Novartis testing facility in Basel, Switzerland, and the (b) (4) facility in Switzerland, DSPTP would not take an action on or before the PDUFA Goal Date of December 27, 2008. Dr. Cox stated that the PDUFA Goal Date would not be extended, instead it would be missed. He further stated that FDA would need more time to complete the review of the materials requested by the Office of Compliance in order to address the deficiencies noted at these sites. Dr. Cox emphasized that the review team will continue to work on the product labeling with Novartis as well as all other aspects of the NDA review.

Anthony Charity from FDA's Office of Compliance had requested that Novartis confirm/clarify the addresses of the (b) (4). The address for (b) (4) in the application was different than the address reported in a 2007 inspection for another product. Novartis agreed to provide information related to the correct address at the teleconference that would occur later in the day.

After Dr. Cox and Mr. Charity made their remarks regarding the foreign manufacturing facilities, these individuals left the teleconference and the scheduled labeling teleconference began and progressed with the remaining personnel from DSPTP and Novartis. Staff from the Office of Compliance organized and provided Novartis staff the necessary information for the teleconference which occurred later in the day.

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Gregory DiBernardo  
Regulatory Project Manager

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/s/

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Joette Meyer

4/6/2009 12:35:40 PM



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on February 6, 2009. The purpose of the teleconference was to discuss concerns related to a recently published paper discussing the efficacy of Coartem in pregnant woman and current and ongoing studies examining the effects of primaquine and Coartem used in combination.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** February 6, 2009  
**APPLICATION NUMBER:** NDA 22-268  
**DRUG NAME:** Coartem® Tablets  
**BETWEEN:**

### Novartis Pharmaceuticals Corporation

Heiner Gruenigner, Ph.D.	Global Program Head, Trop Med Initiatives & EGM
Anne-Claire Marrast, M.D.	Global Program Medical Director
Marc Cousin, Ph.D.	Senior Clinical Trial Head
Paula Rinaldi	Head, U.S. Mature Products, Drug Regulatory Affairs
(b) (4)	
Daniel Stein, M.D.	TM Head, Profiling
Kanan Solanki, Pharm.D.	Fellow

**AND:**

### Food and Drug Administration

Joette Meyer, Pharm.D.	Acting Clinical Team Leader, Office of Antimicrobial Products (OAP)/Division of Special Pathogen and Transplant Products (DSPTP)
Sue Lim, M.D.	Clinical Reviewer-Safety, OAP/DSPTP
Ozlem Belen, M.D.	Clinical Reviewer-Pediatric Safety, OAP/DSPTP
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, OAP/DSPTP
Dakshina Chilukuri, Ph.D.	Clinical Pharmacology Reviewer, OAP/DSPTP
Gregory DiBernardo	Regulatory Project Manager, DSPTP

**SUBJECT:** Discussion on outstanding Clinical concerns for NDA 22-268

### **BACKGROUND:**

Division of Special Pathogen and Transplant Products (DSPTP) recently became aware of a December 23, 2008 publication by Dr. Rose McGready<sup>1</sup> examining the use of a 6 dose regimen of artemether/lumefantrine in pregnant women compared to 7 days of IV artesunate.

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<sup>1</sup> McGready R, Tan SO, Ashley EA, et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated plasmodium falciparum treatment in pregnancy. PLoS Med 2008 Dec 23;5(12):e253

The paper concluded that:

The current standard six-dose artemether-lumefantrine regimen was well tolerated and safe in pregnant Karen women with uncomplicated *P. falciparum* malaria, but efficacy was inferior to 7 day artesunate monotherapy and was unsatisfactory for general deployment in this geographic area. Reduced efficacy probably results from low drug concentrations in later pregnancy. A longer or more frequent AL dose regimen may be needed to treat pregnant women effectively and should now be evaluated. Parasitological endpoints in clinical trials of any antimalarial drug treatment in pregnancy should be extended to delivery or day 42 if it comes later.

This publication was not included in the submissions to NDA 22-268, therefore a teleconference was requested by DSPTP to discuss Novartis's thoughts on Dr. McGready's findings and any plans they may have to conduct or participate in further investigations of the efficacy of Coartem in pregnant women.

Additionally, in an effort to better understand the potential pharmacodynamic interaction of primaquine and Coartem on the QTc interval, DSPTP provided Novartis the reference to a 2007 publication by Krudsood.<sup>2</sup> The Krudsood publication examined patients treated with Coartem who then followed their Coartem treatment sequentially with primaquine treatment. DSPTP wanted to know if Novartis was aware of any ECG safety information from this study or other studies which would assist in determining whether primaquine by itself prolongs the QTc interval or whether Coartem and primaquine administered sequentially have additive effects on the QTc interval.

This information was provided to Novartis informally on February 5, 2009, as an e-mail communication to help facilitate the discussion (e-mail attached below).

## **SUMMARY:**

### **McGready Paper Discussion:**

DSPTP asked Novartis what their thoughts were on the low efficacy rate of artemether/lumefantrine in pregnant women in the McGready paper and what direction, if any do they plan to investigate further the efficacy of Coartem in pregnant women. Novartis stated they believe the efficacy cure rate is low, mainly due to the fact that the patients used were being treated for recrudescence infections. Regarding the low concentrations of lumefantrine, they believe that the exposure to lumefantrine is not different from that observed in non-pregnant patients and that despite the low concentrations, patients were still cured. Novartis does not think the findings of this study warrant further investigation.

DSPTP agrees with this overall assessment and also stated that they did not see any real significant difference in lumefantrine concentrations on Day 7 between patients with recrudescence, novel, and no recurrent infections, as shown in Figure 8 of the paper. DSPTP further commented that there is so much variability in the pharmacokinetics of lumefantrine it

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<sup>2</sup> Krudsood S, Tangpukdee N, Muangnoicharoen S, et al. Clinical efficacy of chloroquine versus artemether-lumefantrine for *Plasmodium vivax* treatment in Thailand. Korean J Parasitol 2007;45(2):111-4/

would be difficult to conclude that pregnant women need a longer treatment course. They also noted that the paper discusses a region and/or population where recrudescence is prevalent; therefore to extrapolate these results to other pregnant women would be difficult to do. It would be difficult to justify conducting a PK study in pregnant women in other parts of the world, when it is not clear what the appropriate PK exposure in pregnant women should be. Novartis stated they concur.

Another point of discussion between Novartis and DSPTP was the notable difference between the timing and method of the assessment of cure in the NDA studies (i.e., day 28 using PCR-unadjusted rates) and the McGready paper (i.e., day 42 using PCR-adjusted rates). These methodological differences make it difficult to conclude that there are differences between the response rates in non-pregnant patients in the NDA studies and pregnant women in the McGready paper. DSPTP pointed out that it is also difficult to assess the PK results reported in the McGready paper, since there are no PK data available from a non-pregnant cohort of women.

DSPTP questioned if Novartis has assessed the efficacy of Coartem at a period of more than 28 days, since the studies submitted to the NDA did not look beyond this time point. DSPTP asked if Novartis was interested in examining this idea further, since it may take more time for pregnant women to clear their parasites based on their physiology. Novartis commented that they have an open dialog with Dr. McGready and Professor Nick White, who was a senior author on the paper, but they do not have any ongoing studies or plans to develop studies at this time.

Novartis commented they have not received any report of lack of efficacy as an AE or SAE. The observational Zambia pregnancy study that was submitted to the NDA was conducted primarily for safety; however, Novartis stated that they would have seen such an AE or SAE if it occurred.

### **Primaquine and Coartem Discussion:**

DSPTP said that the use of primaquine and Coartem still remains an issue because they are not certain what effect primaquine has on the QTc interval. The last version of the label DSPTP sent to Novartis on December 23, 2008, included a statement that <sup>(b) (4)</sup> but this may not be the best option. DSPTP wanted to know if Novartis is aware of any other information published or ongoing that addresses the QTc safety of primaquine alone or in combination with Coartem.

Novartis stated they were aware of an *in vitro* study published in 2002, which demonstrated that primaquine blocks the sodium, but not potassium, channel in cardiac cells. Regarding any clinical data, they did not sponsor the Krudsood paper, and do not have any additional information on whether or not ECGs were obtained in this study beyond what is published in the paper, but did point out that no cardiac AEs were reported. Novartis stated there was also halofantrine study that may be of some interest, but they were not certain if ECG data were included in that publication either.

Other than these studies that were discussed during the teleconference or those sent to Novartis on February 5, 2009, Novartis stated they were not aware of any other data to address cardiac safety of primaquine with or without Coartem. Novartis stated that they object to information in

the label which states that (b) (4) . Instead, they would be willing to accept a statement that physicians should monitor their patients for QTc prolongation.

DSPTP requested Novartis submit all publications discussed for review.

Both DSPTP and Novartis agreed it was helpful to discuss these points and Novartis stated they would submit the studies, as discussed, to the NDA.

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Gregory DiBernardo  
Regulatory Project Manager

**E-mail sent to Novartis on February 5, 2009:**

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**From:** DiBernardo, Gregory  
**Sent:** Thursday, February 05, 2009 10:25 AM  
**To:** 'susan.kummerer@novartis.com'  
**Cc:** 'paula.rinaldi@novartis.com'; 'raffy.chilingirian@novartis.com'; Meyer, Joette M  
**Subject:** NDA 22-268-Coartem-Novartis-Comments/Questions for 2/6/09 Teleconference  
**Importance:** High

Hello Susan,

I have provided the Division's comments for discussion for our scheduled teleconference on February 6, 2009 below. The Division would like to gain a better sense of your perspective on these concerns, but we understand if you do not have a complete response to these topics for the discussion.

**Division Comments:**

1. In December 2008, Dr. Rose McGready published results of a trial of Coartem in pregnant women in which she found that a 6-dose regimen of Coartem was "unsatisfactory for general deployment in this geographic area." We assume you are also aware of this article and we would like to hear your thoughts on her findings and any plans you may have to conduct or participate in further investigations of the efficacy Coartem in pregnant women.

Reference: *McGready S, Tan SO, Ashley EA, et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated Plasmodium falciparum treatment in pregnancy. PLOS medicine 2008;5(12):1699-1715.*

2. In patients with *P. vivax* malaria, primaquine should be given following Coartem in order to provide radical care. The lumefantrine component of Coartem is known to produce small effects on the QT interval, such that it will be labeled not to be used within 30 days of quinine, another QT prolonging drug. The quinoline antimalarials, including quinine, primaquine, etc. are known to be cardiotoxic. Not much information is available regarding primaquine, but it has been shown to have class I activity (i.e., it effects myocardial depolarization). While it does not appear to produce overt cardiotoxicity, little is known about it's effects on the QT interval in patients and especially in those receiving other QT prolonging drugs. (b) (4)

However, in treating vivax malaria, it may not be in the patient's best interest to delay primaquine treatment for 30 days. In a publication by Krudsood in 2007, treatment with Coartem was followed sequentially with primaquine treatment. Are you aware of any ECG safety information from this study or others which can help determine whether primaquine by itself prolongs the QT interval or whether Coartem and primaquine administered sequentially have additive effects on the QT interval?

References:

*White NJ. Cardiotoxicity of antimalarial drugs. Lancet Infectious Diseases 2007;7:549-58.*

*Krudsood S, Tangpukdee N, Muangnoicharoen S, et al. Clinical efficacy of chloroquine versus artemether-lumefantrine for Plasmodium vivax treatment in Thailand. Korean Journal of Parasitology. 2007;45:111-4.*

Please let me know if you have questions.

Thank you,

**Gregory F. DiBernardo**  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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/s/

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Joette Meyer  
3/30/2009 12:36:20 PM



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products**

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**TRANSMITTAL SHEET**

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**DATE:** March 24, 2009

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via E-mail	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
E-mail: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem®-Providing Postmarketing Requirements for NDA 22-268 to Novartis for Final Agreement

**Total no. of pages including cover:** 8

**Comments: Concurrence**

Joette Meyer, Pharm.D.,  
Diana Willard

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**Document to be mailed:**             YES             NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1600. Thank you.

Dear Ms. Kummerer,

In order to assist with the completion of the review of NDA 22-268, please provide your final agreement and concurrence to the information listed below.

We request you submit to the NDA, as an official submission, your stated agreement to each of the Postmarketing Requirements identified below. We further request that your agreement identify each Postmarketing Requirement specifically and completely.

Please be aware, that due to time constraints involved in this NDA review, we ask you submit a complete, official response to this request no later than March 26, 2009.

**1. Conduct a descriptive study of the use of Coartem Tablets in non-immune travelers.**

For a period of five years following approval, collect baseline patient demographic information (including age, weight, height, sex, race, prior medications and concomitant medications, as well as immune status), adverse reactions, including potential nervous system and cardiac adverse reactions, and efficacy outcomes. You should include representation of adults > 65 years, children ≤ 16 years, and overweight patients (BMI ≥ 25 kg/m<sup>2</sup>). Submit yearly reports summarizing data on patients treated with Coartem Tablets within the previous year and the final report integrating information on all patients in the Final Report Submission.

The timetable you submitted on <<insert date>> states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by March 2010
Study Start Date:	by October 2010
Final Report Submission:	by April 2016

**2. Submit surveillance reports to evaluate the potential development of resistance to Coartem Tablets.**

For a period of five years following approval, submit a yearly report describing the reported resistance to a combination of artemether and lumefantrine in malaria endemic countries as obtained from ongoing resistance monitoring programs on antimalarials collected by international consortia and organizations (e.g., World Health Organization).

The timetable you submitted on <<insert date>> states that you will fulfill this requirement according to the following timetable:

Submission of Study Report Plan:	by July 2009
Study Reporting Start Date:	by October 2009
Final Report Submission:	by August 2016

**3. Conduct a neurotoxicity study of oral artemether in juvenile rats including neurologic functional batteries, toxicokinetics, and extensive brain histopathology.**

Conduct a neurotoxicity study of oral artemether in juvenile rats to assess how exposure and toxicity in young animals compares with older animals and humans, and whether neurologic deterioration occurs following the terminal dose. This study should consist of a main study group, a toxicokinetic group, and a recovery group. In this study, comprehensive histopathological examination of the central nervous system should be conducted.

The timetable you submitted on <<insert date>> states that you will conduct this study according to the following timetable:

Final Protocol Submission: by July 2009  
Study Start Date: by December 2009  
Final Report Submission: by December 2011

**4. Conduct bacterial reverse mutation studies (Ames assays) for lumefantrine impurities<sup>(b) (4)</sup> and<sup>(b) (4)</sup> and artemether impurities<sup>(b) (4)</sup>**

Lumefantrine impurities<sup>(b) (4)</sup> and artemether impurities<sup>(b) (4)</sup> have structural alerts for genotoxicity, and the proposed release limits for these compounds are higher than levels that are qualified by available toxicology studies.

The timetable you submitted on <<insert date>> states that you will conduct this study according to the following timetable:

Study Start Date: by December 2009  
Final Report Submission: by June 2010

**5. Perform spectral characterization of all specified impurities for lumefantrine impurities<sup>(b) (4)</sup> and artemether impurities<sup>(b) (4)</sup>**

The structure of lumefantrine impurities<sup>(b) (4)</sup> and artemether impurities<sup>(b) (4)</sup> should be characterized using spectral procedures such as <sup>1</sup>H- and <sup>13</sup>C-NMR (nuclear magnetic resonance), infrared (IR), ultraviolet and mass spectroscopy. Tabulated, interpreted data for all spectra, and copies of IR and <sup>1</sup>H-NMR spectra should be submitted.

The timetable you submitted on <<insert date>> states that you will conduct this study according to the following timetable:

Study Start Date: by June 2009  
Final Report Submission: by December 2009

**6. Conduct an *in vitro* study to characterize the induction potential of artemether, dihydroartemisinin (DHA), and lumefantrine on the metabolism of substrates of CYP3A.**

Conduct an *in vitro* study to evaluate the induction potential of artemether, DHA, and lumefantrine on the metabolism of co-administered drugs that are substrates of the Cytochrome P450 3A4 (CYP3A4) enzyme system (e.g., oral contraceptives). Refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* (<http://www.fda.gov/cder/guidance/6695dft.pdf>) for details on the conduct of the *in vitro* study.

If the results of this *in vitro* study are positive, a clinical trial will be needed to further assess this risk (see Item 14, below).

The timetable you submitted on <<insert date>> states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by December 2009
Study Start Date:	by March 2010
Final Report Submission:	by March 2011

**7. Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine, the components of Coartem Tablets, and rifampin.**

If, upon review, it is determined that the clinical trial discussed in Item 11 below adequately addresses the potential interaction between artemether and lumefantrine and rifampin, then this *in vitro* study will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* for details on the conduct of the *in vitro* study.

The timetable you submitted on <<insert date>> states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 2011
Study Start Date:	by January 2012
Final Report Submission:	by January 2013

**8. Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine, the components of Coartem Tablets, and protease inhibitors (PIs).**

If, upon review, it is determined that the clinical trial discussed in Item 12 below adequately addresses the potential interaction between artemether and lumefantrine and PIs, then this *in vitro* study will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* for details on the conduct of the *in vitro* study.

The timetable you submitted on <<insert date>> states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 2011
Study Start Date:	by January 2012
Final Report Submission:	by January 2013

**9. Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine, the components of Coartem Tablets, and non-nucleoside reverse transcriptase inhibitors (NNRTIs).**

If, upon review, it is determined that the clinical trial discussed in Item 13 below adequately addresses the potential interaction between artemether and lumefantrine and NNRTIs, then this *in vitro* study will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling* for details on the conduct of the *in vitro* study.

The timetable you submitted on <<insert date>> states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by June 2011
Study Start Date:	by January 2012
Final Report Submission:	by January 2013

Finally, we have determined that only clinical trials (rather than an observational study) will be sufficient to assess the signal of serious risk of auditory dysfunction or identify an unexpected serious risk arising from treatment failure of Coartem Tablets due to altered metabolism by co-administered drugs or drug-drug interactions.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trials:

**10. Complete the currently ongoing trial “An open label, single center study of the effects of Coartem, Malarone and artesunate-mefloquine on auditory function following the treatment of acute uncomplicated *P. falciparum* malaria in patients 12 years of age or older in Columbia.”**

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Trial Start Date:	ongoing
Final Report Submission:	by March 2010

**11. Complete a clinical drug interaction trial to evaluate the effect of a co-administered CYP3A4 inducer on the pharmacokinetics of artemether and lumefantrine, the components of Coartem Tablets.**

Complete a clinical drug interaction trial using a potent CYP3A4 inducer, such as rifampin, to evaluate the effect of co-administering the inducer on the pharmacokinetics of artemether and lumefantrine. If, upon review, it is determined that the trial adequately addresses the potential interaction between artemether and lumefantrine and rifampin, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and rifampin will not be needed (see Item 7 above).

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Protocol Submission:	by June 2009
Trial Start Date:	ongoing
Final Report Submission:	by March 2011

**12. Complete a clinical drug interaction trial to evaluate the two-way interaction between artemether and lumefantrine, the components of Coartem Tablets, and a protease inhibitor (PI).**

Complete a clinical drug interaction trial using a representative PI, such as lopinavir/ritonavir or ritonavir, to evaluate the two-way interaction between artemether and lumefantrine and a PI. If, upon review, it is determined that the trial adequately addresses the potential interaction between artemether and lumefantrine and PIs, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and a PI will not be needed (see Item 8 above).

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Protocol Submission:	by June 2009
Trial Start Date:	ongoing
Final Report Submission:	by March 2011

**13. Complete a clinical trial to evaluate the two-way interaction between artemether and lumefantrine, the components of Coartem Tablets, and a non-nucleoside reverse transcriptase inhibitor (NNRTI).**

Complete a clinical drug interaction trial using a representative NNRTI, such as efavirenz or nevirapine, to evaluate the two-way interaction between artemether and lumefantrine and a NNRTI. If, upon review, it is determined the trial adequately addresses the potential interaction between artemether and lumefantrine and NNRTIs, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and an NNRTI will not be needed (see Item 9 above).

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Protocol Submission:	by June 2009
Trial Start Date:	ongoing
Final Report Submission:	by March 2011

**14. Conduct a clinical interaction trial to evaluate the induction potential of artemether and lumefantrine, the components of Coartem Tablets, on CYP3A4 substrates.**

If the results of the *in vitro* study (see Item 6 above) are positive, a clinical trial will be needed to further characterize the effect of artemether and lumefantrine on the pharmacokinetics of co-administered drugs that are metabolized by the CYP3A4 enzyme system, such as oral contraceptives.

The timetable you submitted on <<insert date>> states that you will conduct this *in vivo* study, if needed, according to the following timetable:

Final Protocol Submission:	by June 2011
Trial Start Date:	by October 2011
Final Report Submission:	by October 2012

If you have any questions regarding this communication, please contact me at 301-796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo  
3/24/2009 04:53:29 PM  
CSO

Postmarketing Requirements to Novartis for Final Agreement for NDA  
22-268



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Antimicrobial Products

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**TRANSMITTAL SHEET**

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**DATE:** March 24, 2009

<b>To:</b> Susan Kummerer, M.S.	<b>From:</b> Mr. Gregory F. DiBernardo Regulatory Project Manager
<b>Company:</b> Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Transplant Products
<b>Fax number:</b> Transmittal sent via E-mail	<b>Fax number:</b> 301-796-9881
<b>Phone number:</b> 862-778-1130	<b>Phone number:</b> 301-796-1600
E-mail: susan.kummerer@novartis.com	

**Subject:** NDA 22-268-Coartem®-Providing Postmarketing Commitments for NDA 22-268 to Novartis for Final Agreement

**Total no. of pages including cover:** 3

**Comments: Concurrence**

Joette Meyer, Pharm.D.,

Diana Willard

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**Document to be mailed:**             YES                             NO

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Dear Ms. Kummerer,

In order to assist with the completion of the review of NDA 22-268, please provide your final agreement and concurrence to the information listed below.

We request you submit to the NDA, as an official submission, your stated agreement to the Postmarketing Commitment identified below. We further ask that your agreement identify this Postmarketing Commitment specifically and completely.

Please be aware, that due to time constraints involved in this NDA review, we ask you submit a complete, official response to this request no later than March 26, 2009.

**1. Develop a dissolution test method for Coartem Tablets to achieve a minimum (b) (4) dissolution of each component, artemether and lumefantrine.**

Develop a test method to achieve (b) (4) dissolution of each component in Coartem Tablets, artemether and lumefantrine, through the proposed shelf life. If possible, one dissolution test method should be developed for both components. Two yearly interim reports should also be submitted.

The time table << insert date >> states that you will conduct this study according to the following timetable:

Study Start:	by June 2009
Interim Report Submissions:	June 2010, June 2011
Final Report Submission:	by December 2011

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Gregory F DiBernardo  
3/24/2009 04:56:36 PM  
CSO

Postmarketing Commitments to Novartis for Final Agreement for NDA  
22-268



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on October 30, 2008. The purpose of the teleconference was to discuss Office of New Drug Quality Assurance information requests dated October 9, 2008 and October 28, 2008.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Dorota Matecka, Ph.D.  
Chemistry Reviewer  
Office of New Drug Quality Assurance  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** October 30, 2008

**APPLICATION NUMBER:** NDA 22-268

**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

**Novartis Pharmaceuticals Corporation**

Joan Materna

Dev-Global Regulatory CMC

**AND:**

**Food and Drug Administration**

Dorota Matecka, Ph.D.

Chemistry Reviewer, Office of New Drug Quality Assurance,  
(ONDQA)

Shrikant Pagay, Ph.D.

Chemistry Reviewer, ONDQA

Gregory DiBernardo

Regulatory Project Manager, Division of Special Pathogen and  
Transplant Products, (DSPTP)

**SUBJECT:** Explanation of ONDQA Facsimile Requests dated October 9, 2008 and October 28, 2008

**BACKGROUND:**

The Office of New Drug Quality Assurance (ONDQA) review team requested an informal e-mail communication be sent, outlining a request for information from Novartis Pharmaceuticals Corporation (Novartis) on October 3, 2008. An official facsimile (fax) request was sent to Novartis on October 9, 2008; it included the same items from the e-mail communication of October 3, 2008, but added an additional request, labeled Question #13. A brief teleconference between Novartis and the ONDQA reviewers was held on October 21, 2008 to address Question #13 from the October 9, 2008 fax. Due to the timeline of this Priority Review NDA the ONDQA reviewers requested a teleconference to discuss outstanding material with Novartis. On October 30, 2008 Novartis agreed to another teleconference to address and up date the outstanding requests in the October 9, 2008 fax and the newly requested October 28, 2008 ONDQA fax. Novartis stated that providing impurities data on clinical batches has been a challenge because many parts of this NDA application are part of a global dossier, which has complicated the process. Novartis also stated they are doing their best on getting certificates of analysis and information on impurities, but since much of the information is over 10 years old, it is yet another challenge.

**SUMMARY:**

Since the purpose of this teleconference was to present available information prior to an official submission to the NDA, the summary of this teleconference will be Novartis's and ONDQA responses to both the October 9, 2008 and October 28, 2008 faxes in bold italic font following the fax questions.

**October 9, 2008 facsimile questions:**

1. Please propose an assay test (analytical procedure and acceptance criteria) in the specification of dihydroartemisinin.  
*This request has been problematic, since it has been difficult to get specification of dihydroartemisinin, Novartis will try to justify why specification is not needed.*
2. State if the analytical procedure (HPLC) used for reporting the impurities in the artemether crude and artemether drug substance specifications is capable of detecting the two epimers of dihydroartemisinin and the impurity of the artemisinin starting material (b) (4).  
*Novartis confirms 1 HPLC method is used not 2 it is the same for artemether crude and arthemether drug substance. Novartis will have to update ONDQA to see if HPLC is capable of detecting 2 epimers.*
3. Information provided in section 3.2.S.2.6, Table 2-1. Summary of synthesis modifications includes a statement that the reduction of (b) (4) of artemisinin (at the (b) (4) site) affords (b) (4) of dihydroartemisinin. Please explain this mass balance.  
*Novartis is waiting for information from the (b) (4) facility, Novartis thinks it is a typographical error, but will confirm.*
4. Confirm that all the batches of lumefantrine listed in Tables 3.1-3.4 were analyzed for all the impurities listed using the analytical procedure currently proposed for the lumefantrine drug substance. Please provide the limit of detection.  
*Novartis states all batches were examined for all impurities in the referenced tables, they will confirm the limit of detection and update ONDQA.*
5. Provide information on levels of impurities (other than (b) (4)) observed for batches of lumefantrine manufactured at the (b) (4) facility.  
*Novartis stated they are waiting for (b) (4) Facility to provide this information, they will update ONDQA when this information becomes available. ONDQA made note that in a separate e-mail request after the October 21, 2008 teleconference, they requested information on artemether as well as lumefantrine.*
6. Considering very low water solubility of both drugs, please explain if any efforts were made in increasing the drug solubility other than (b) (4) for the development of the tablet formulation.  
*Novartis indicated they had performed experiments to see whether changing disintegrant level in the (b) (4) tablet disintegration and dissolution.*
7. Provide test methods and the data for the compatibility studies of the binary mixtures of the two drugs and excipients.  
*Novartis stated TLC testing against a number of common excipient data will be submitted. Novartis will provide this data on stressed and unstressed samples.*
8. Several unit operations are required in manufacturing the tablets, each with controlled operating parameters (in-process parameters for operating the equipment) and in-process controls (b) (4). Please propose in-process controls for the (b) (4) the currently proposed in-process controls include only (b) (4).  
*The ranges have not been registered in the past, so if Novartis includes them at this time, it will require regulatory action. Novartis will have to look into this further.*
9. Provide data to support the absence of artemether polymorph B in Coartem tablets.  
*Novartis will provide response as formal submission, in summary Polymorph A does not convert into Polymorph B below 50°C. ONDQA requested to see if data has been generated at the development stage for Coartem® tablets.*

10. Please confirm if a failed batch will be reprocessed or reworked?

*Novartis provided the response that they do not reprocess or rework failed batches.*

11. Include USP disintegration test and specification for Coartem tablets for release and shelf life (we expect to have further comments on the dissolution test).

*Novartis stated that a method can be developed to address this request, but they can only make a commitment to try. They do not have issues with developing a test, but they would need time to complete this request.*

12. The Division requested the following information in an August 28, 2008 Facsimile:

Identify the same tests in the corresponding validation report by specifying the page number from the Table of Contents for Module 3.2 – Body of Data. (corresponds to the registered and alternate test methods)

You provided a response to this request on September 15th, however because there were no page numbers on the PDF files you submitted in the CMC sections of the original NDA, it is very difficult to locate this information. The page numbers for the validation test methods provided in the September 15<sup>th</sup> submission do not correspond to those pages in the CMC sections of the original NDA submission. Since multiple tests methods are proposed in the drug product specifications for identification, assay, degradation products, and for dissolution testing, it is very difficult to find the corresponding test methods in the validation reports.

**Please expedite your response for the following information:**

For each analytical procedure, including identification, assay, degradation products and dissolution test, provide a combined document containing the proposed analytical procedure and a corresponding validation report.

*Novartis will be providing this information as official submission, to be sent to the FDA Gateway. ONDQA commented that while they understand there are multiple methods, they are unsure about the overall strategy on how a primary and/or an alternate method would be selected and used by Novartis.*

13. The stability section is compiled from several study reports labeled as registration batches, annual batches, post approval study batches, etc., which appears to be based on studies conducted for registration under a WHO program before this NDA submission. Please provide the following information to expedite review of this data:

Provide page numbers from the original NDA submission for the study protocol, study reports, and stability data for:

Registration Batches for US NDA in (b) (4) bottles with child resistant closures.  
Registration Batches for US NDA in Blister package.  
Supportive Study Batches for US NDA in (b) (4) bottles with or without child resistant closures.  
Supportive Study Batches for US NDA in Blister package.  
Batches used in Statistical analysis of the data. Specify if the batches used for analysis are registration batches or supportive batches.

*Novartis provided a response to Question #13 to ONDQA reviewers during an October 21, 2008 teleconference. The response was officially submitted to the NDA on November 6, 2008.*

**October 28, 2008 facsimile questions:**Drug Substance*Artemether Drug Substance:*

1. Please provide details regarding the (b) (4) equipment and in-process controls employed in the (b) (4) process of artemether drug substance.  
***Novartis stated the information is being obtained. Novartis indicated no in-process controls were employed during the (b) (4) process, they will provide data in an official submission.***
2. Please provide data demonstrating that the proposed re-work procedure in the manufacturing process of artemether produces the drug substance of acceptable quality.  
***Novartis stated they have data on three batches constituted with material that was reworked.***
3. The Appendix 5.3 of section 3.2.S.3.2 includes a representative HPLC chromatogram of artemether drug substance spiked with impurities: (b) (4). Please explain why a (b) (4) analytical procedure, is proposed for the determination of the two impurities, (u) (4) in the artemether specification.  
***Novartis stated not all impurities have chromophores, they are waiting to receive a proper description, they will follow up on providing materials.***
4. Please provide a proof of identity (i.e. spectral data) for impurities identified in artemether drug substance.  
***Novartis stated they were having difficulties, they are looking for the information, but it is a challenge at this point in time.***
5. Please provide a justification for the proposed acceptance criteria for polymorph A content (NLT (b) (4)) and particle size (b) (4) in the artemether drug substance specification; i.e. please provide respective data for the batches used in the pivotal clinical studies and stability batches.  
***Novartis stated that Polymorph A=(b) (4), they have people looking for certificate of analysis and looking at particle size. They will have to get back to ONDQA on this issue.***  
***ONDQA stated the October 8, 2008 submission only contained impurities, not particle size.***
6. You have stated that the synthetic process of artemether drug substance has not changed during the entire product development. Please explain the statement on page 28 of the Stability Report CD-ART/a/STA/5 entitled Artemether (CGP 56 696): "the drug substance produced using the synthesis intended for market is more stable than those produced using the synthesis intended for clinical research."  
***Novartis stated that all batches come from same site and process, they are in the process of clarifying all information for any changes in the facility but not in synthesis.***

*Lumefantrine Drug Substance:*

7. Please provide details regarding the (b) (4) equipment and in-process controls employed in the (b) (4) process of lumefantrine drug substance.  
***Novartis stated it uses standard (b) (4) equipment. ONDQA asked Novartis to identify (b) (4) information.***
8. The acceptance criteria for related substances in the specifications of the intermediates 3 and 4 in the synthesis of lumefantrine appear very wide. Consequently, the assay acceptance criteria for these intermediates appear very low (NLT (b) (4) and NLT (b) (4) respectively). Please provide typical release data for these intermediates and explain relatively high yields reported for those steps.  
***Novartis stated they will update this information when it is available.***  
***ONDQA stated the yield is quite high for each step, how do you evaluate the yield?***
9. Please provide information regarding the biological activity of Z- and E isomers of lumefantrine. In addition, provide data on the ratio of these two isomers in batches of lumefantrine and artemether tablets used in pivotal clinical studies.

***Novartis is examining to see if the work was ever completed. Novartis stated if it was done using a current technique they expect to see a Z-isomer.***

10. Please clarify the code names of the lumefantrine impurities, e.g. (b) (4). Indicate which structure represents isomer (b) (4). Note that these are constitutional isomers, not stereoisomers.

***Novartis stated (b) (4) is no longer found in the drug substance.***

***ONDQA asked Novartis to please clarify which is the A and B code names for (b) (4) impurities.***

11. Please provide a proof of identity (i.e. spectral data) for impurities identified in lumefantrine drug substance.

***Novartis stated they are still in the process of looking for the information to address Question #11, they will have to follow up on this question.***

12. Please provide a justification for the proposed acceptance criteria for particle size in the lumefantrine drug substance specification, i.e. please provide respective data for the batches used in the pivotal clinical studies and stability batches. Please revise the proposed acceptance criteria to include (b) (4) limits.

***Novartis is looking for information on particle size data, they have a concern about changing particle size limits because it is a globally registered specification, so they will have to update ONDQA on this question.***

#### Drug Product

13. Include testing at 6 months time point for Annual batch testing in Study protocol: Table 2-1 in STP\_07.524.01 in the submission.

***Novartis stated that 6month time point is dropped for products with a (b) (4) month expiry date, ONDQA stated for Novartis to add a 6 month time period and drop, if necessary, the 18 month time point if the product stability is monitored for (b) (4) months.***

***Novartis stated they will have to discuss this request with other Novartis CMC staff.***

14. Although adequate sink condition is achieved in dissolving Artemether (solubility of artemether in water at 25°C is 0.13 g/L), the tablet dissolution is very slow i.e.,  $Q = \frac{(b) (4)}{b}$  in (b) (4) hours. Please explain. Revise the procedure to at least  $Q = \frac{(b) (4)}{b}$  dissolved.

***Novartis is compiling all the dissolution data to reassess if the data supports meeting a  $Q = \frac{(b) (4)}{b}$  specification. They will provide ONDQA a counter proposal for this question.***

15. The assay values for both drugs in Coartem tablets at release are approximately (b) (4) below the label claim; please explain if the low assay values at release are related to losses during the manufacturing process.

***Novartis stated they are meeting internally to provide a response for this question.***

16. The individual and total unknown degradation products for artemether in clinical batches # 502 and # 16/995/5 exceed the proposed specifications for impurity identification. Please identify the individual unknown impurities that are greater than the ID threshold.

***Novartis asked if ONDQA could provide the specific time points from the stability data for the above clinical batches.***

17. No data was provided for (b) (4) and (b) (4) impurities of artemether in the clinical batches # 509 and # 16/995/5. Please explain.

***ONDQA confirmed it was refereeing to batch #502, not #509 in this question. ONDQA agreed to provide reference for stability to address this question.***

***Novartis stated this material can be found in Tables 2 and 3 from the May 14, 2008 submission to the NDA.***

**ACTION ITEMS:**

Novartis agreed to the following items:

- To submit the discussed responses officially to the NDA for both the October 9, 2008 and October 28, 2008 faxes by November 5, 2008.
- Novartis agreed they will work to have most of the responses completely answered, but they may need more time to provide all information
- Novartis will provide the stability information for artemether for the (b) (4) facility as was previously requested during the October 21, 2008 teleconference
- Novartis agreed to officially submit its response for Question #12 from the October 9, 2008 fax by the end of the week
- Novartis agreed to provide stability information for Question #17 from the October 28, 2008 fax
- Novartis agreed to investigate the request by Dr. Matecka to address the corrections needed for the facility in Cork Ireland that were recently identified.

ONDQA agreed to the following items:

- ONDQA will identify what is the reference for stability for Question #16 from the October 28, 2008 fax
- ONDQA will identify the reference points for Question #17 from the October 28, 2008 fax
- Dr. Matecka explained the situation in Cork, Ireland and stated that FDA was notified by a representative from Novartis that the name of the API testing facility is Novartis International Pharmaceutical Ltd., Branch Ireland International Services Laboratory ("ISL"), Ireland and not (b) (4) as stated in the original NDA submission by the applicant. It was further explained that International Services Lab Novartis International Pharmaceutical Ltd. shares the building with the Novartis manufacturing facility but is considered a different corporate entity. This correction had to be made in the EER submitted for this NDA.

**ADDENDUM:**

Please note that ONDQA provided its requested Action Items to Novartis via e-mail communication on October 31, 2008. (e-mail attached below)

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**From:** DiBernardo, Gregory  
**Sent:** Friday, October 31, 2008 2:56 PM  
**To:** 'joan.materna@novartis.com'  
**Cc:** 'susan.kummerer@novartis.com'; Pagay, Shrikant N; Matecka, Dorota M  
**Subject:** NDA 22-268-Coartem-Novartis-Action Items from 10/30/08 CMC Teleconference

Hello Ms. Materna,

We are providing the action items from our 10/30/08 Teleconference between the DSPTP and Novartis. Below are the requested items to address questions #16 and #17 from our 10/28/08 CMC facsimile request.

**Reference for the degradation products in the 2 clinical batches (502 and 16/995/5). The stability data is reported under Registration stability Report Ident. 158528.7/ and report RSR6500A in Module 3 Stability section.**

Please let me know if you need any additional information.

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue

NDA 22-268

Page 8

Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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Gregory DiBernardo  
Regulatory Project Manager

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/s/

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Dorota Matecka  
3/4/2009 07:20:03 AM



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on October 1, 2008. The purpose of the teleconference was to provide clarification on the request for preclinical tables which was stated in 74-Day Filing Letter for NDA 22-268.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Owen McMaster, Ph.D.  
Pharmacology/Toxicology Reviewer  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes



studies may be known. Novartis stated these studies without batch numbers will be included and identified at the end of the submitted table.

Novartis agreed they now had a complete understanding of what DSPTP was requesting and would work to provide this material in a timely manner as an official submission to the NDA.

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Gregory DiBernardo  
Regulatory Project Manager

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/s/

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Owen McMaster  
2/27/2009 11:18:22 AM



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on October 15, 2008. The purpose of the meeting was to provide advice on your December 3, 2008 Advisory Committee Meeting Presentation for NDA 22-268.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Meeting Minutes

**MEMORANDUM OF MEETING MINUTES****MEETING DATE:** October 15, 2008**TIME:** 9:30 a.m.**APPLICATION:** NDA 22-268**DRUG NAME:** Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets**TYPE OF MEETING:** Advice**MEETING CHAIR:** Joette Meyer, Pharm.D.**MEETING RECORDER:** Gregory DiBernardo**FDA ATTENDEES:** (Title and Office/Division)

Renata Albrecht, M.D.	Division Director, OAP/Division of Special Pathogen and Transplant Products (DSPTP)
Joette Meyer, Pharm. D.	Acting Clinical Team Leader, OAP/DSPTP
Elizabeth O'Shaughnessy, M.D.	Clinical Reviewer-Efficacy, OAP/DSPTP
Sue Lim, M.D.	Clinical Reviewer-Safety, OAP/DSPTP
Ozlem Belen, M.D.	Clinical Reviewer-Pediatric Safety, OAP/DSPTP
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader, OAP/DSPTP
Dakshina Chilukuri, Ph.D.	Clinical Pharmacology Reviewer, OAP/DSPTP
William Taylor, Ph.D.	Pharmacology Toxicology Team Leader, OAP/DSPTP
Owen McMaster, Ph.D.	Pharmacology Toxicology Reviewer, OAP/DSPTP
Rama Dwivedi, Ph.D.	Pharmacology Toxicology Reviewer, OAP/DSPTP
Terry Miller, Ph.D.	Pharmacology Toxicology Reviewer, OAP/DSPTP
Shukal Bala, Ph.D.	Microbiology Team Leader, OAP/DSPTP
Aaron Ruhland, Ph.D.	Microbiology Reviewer, OAP/DSPTP
Simone Shurland, Ph.D.	Microbiology Reviewer, OAP/DSPTP
Karen Higgins, ScD.	Biostatistics Team Leader, OAP/DSPTP
Xianbin Li, Ph.D.	Biostatistics Reviewer, OAP/DSPTP
Lan Zeng, M.A.	Biostatistics Reviewer, OAP/DSPTP
Norman Schmuff, Ph.D.	Branch Chief, Office of New Drug Quality Assurance (ONDQA)
Dorota Matecka, Ph.D.	Chemistry Reviewer-Drug Substance, ONDQA
Shrikant Pagay, Ph.D.	Chemistry Reviewer-Drug Product, ONDQA
Yulia Yasinskaya, M.D.	Clinical Reviewer, OAP/DSPTP
Tafadzwa Vargas-Kasambira, M.D.	Clinical Reviewer, OAP/DSPTP
Hala Shamsuddin, M.D.	Clinical Reviewer, OAP/DSPTP
Ying Mu, M.D., Ph.D.	Pharmacology Toxicology Reviewer, OAP/DSPTP
Diana Willard	Chief, Project Management Staff, OAP/DSPTP
Gregory DiBernardo	Regulatory Project Manager, OAP/DSPTP

**EXTERNAL CONSTITUENT ATTENDEES:**

Heiner Gruenigner, Ph.D.	Global Program Head, Trop Med Initiatives & EGM
Anne-Claire Marrast, M.D.	Global Program Medical Director
Marc Cousin, Ph.D.	Senior Clinical Trial Head
John Orloff, M.D.	Head U.S. Medical and Drug Regulatory Affairs
Paula Rinaldi	Director, Drug Regulatory Affairs
Susan Kummerer, M.S.	Director, Drug Regulatory Affairs
Margaret Weaver, Ph.D.	Principal Fellow
Fanny Ki, Ph.D.	Group Head Biostatistics
Chin Koerner	Novartis Liaison Office, Rockville, MD
Kanan Solanki, Pharm.D.	Fellow

**Via Teleconference United States**

Joel Morganroth, M.D.	University of California, San Francisco School of Medicine
-----------------------	--

**Via Teleconference Basel, Switzerland**

Darine Ghanem, Pharm.D.	Expert Clinical Manager
-------------------------	-------------------------

(b) (4)

Caterina Capaccioli	Senior Project Manager
Martine Foureur, M.D.	Therapeutic Area Safety Leader

**BACKGROUND:**

During a July 25, 2008, teleconference with Novartis Pharmaceuticals Corporation (Novartis) regarding Coartem®, the Division of Special Pathogen and Transplant Products (DSPTP) asked if Novartis would be interested in sharing with DSPTP copies of their draft Background Book as well as the material they planned to present at the Advisory Committee (AC) scheduled for December 3, 2008. Novartis stated that such a presentation would be useful and they agreed to do so. On September 25, 2008, via facsimile transmission, DSPTP provided recommendations to Novartis regarding topics/issues to address in the material for the AC. The draft Background Book containing Novartis's slides was submitted to the Division on October 6, 2008. It was agreed that Novartis would present the Clinical Efficacy and Clinical Safety Portions of their AC slide presentations to DSPTP on October 15, 2008, during a face-to-face meeting.

**MEETING OBJECTIVE:**

The meeting objectives were for Novartis to preview their AC presentations to DSPTP prior to finalizing the presentations for the December 3, 2008 Advisory Committee meeting. Novartis also agreed to submit a draft Background Book to DSPTP in advance of the face-to-face meeting. Finally, the Division agreed to provide feedback to Novartis so that they could finalize their presentations and Background Book.

**MEETING:**

Following introductions from both Novartis and DSPTP and a brief synopsis of the meeting background, the meeting began with Dr. Marrast from Novartis presenting the Clinical Development Efficacy portion of the slide presentation (slides CC-1-CC-45 attached). After Dr. Marrast completed the presentation on Clinical Development Efficacy she then began the presentation on Clinical Safety (slides CE-1-CE-14 attached).

After Dr. Marrast had completed these two presentations DSPTP opened the discussion by providing their questions and comments.

While Novartis did not intend to present their Risk-Benefit presentation, DSPTP did request if Dr. Marrast could provide a brief overview of this material at this time. Novartis agreed to present this material, but stated it had not been rehearsed and the slides did not have all the necessary updates (slides CB-1-CB-11 attached).

Following Dr. Marrast's presentation on Risk Benefits, DSPTP provided additional comments.

**DECISIONS (AGREEMENTS) REACHED:**

- Novartis agreed to address the points made by DSPTP during the meeting for inclusion in their final Background Book to be sent to FDA Advisors and Consultants Staff.
- DSPTP indicated it was their intent to complement, not duplicate, the topics covered by Novartis during their AC presentation.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

None

**ACTION ITEMS:**

- The Division stated they will provide Novartis any additional comments regarding the slides or Background Book within one week via facsimile transmission.
- Novartis agreed to incorporate the suggested edits made by the FDA during this presentation and to submit to the NDA a hard copy version of the Final Background Book at the time of submission to the FDA Advisors and Consultants Staff.

**ATTACHMENTS/HANDOUTS:**

Slides from presentations are attached

69 Page(s) Withheld

X Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

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/s/

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Joette Meyer  
2/26/2009 02:15:12 PM



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on November 7, 2008. The purpose of the teleconference was to clarify why the Division of Scientific Investigation (DSI) requested a Teleconference on November 12, 2008.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** November 7, 2008

**APPLICATION NUMBER:** NDA 22-268

**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

### **Novartis Pharmaceuticals Corporation**

Mathias Hukkelhoven, Ph.D.  
John Orloff, M.D.

Senior Vice President, Global Head, Drug Regulatory Affairs  
Head U.S. Medical and Drug Regulatory Affairs

**AND:**

### **Food and Drug Administration**

Renata Albrecht M.D.

Director, Division of Special Pathogen and Transplant Products,  
(DSPTP)

Joette Meyer, Pharm. D.

Acting Clinical Team Leader, DSPTP

Gregory DiBernardo

Regulatory Project Manager, DSPTP

**SUBJECT:** Clarify why the Division of Scientific Investigation (DSI) Requested a Teleconference on November 12, 2008.

### **BACKGROUND:**

Due to concerns raised by Division of Scientific Investigation (DSI) during a recent site inspection of the Global Headquarters for Novartis Pharmaceuticals Corporation (Novartis), DSI requested a teleconference with Novartis Regulatory Affairs and Quality Assurance Staff on November 12, 2008. The Division of Special Pathogen and Transplant Products, (DSPTP) agreed to coordinate this teleconference. The teleconference request and its close timing to ongoing clinical site inspections in Africa, Thailand, and a Headquarter inspection in Switzerland prompted Novartis to request a brief teleconference prior to the teleconference requested by DSI to better understand why it was being requested.

### **SUMMARY:**

DSPTP informed Novartis the teleconference requested by DSI for November 12, 2008 was not to discuss any findings during the recent clinical site inspections in Africa or Thailand or the Novartis Headquarters inspection, but was to discuss a misunderstanding of the procedures followed during the Basel, Switzerland Headquarters inspection. DSI wanted to again emphasize these inspections are critical to planning the Advisory Committee Meeting in December 2008 and to the review of NDA 22-268; as well as express concerns raised during the recent Novartis Headquarters inspection.

The Project Manager discussed the reasons for the teleconference requested by DSI earlier in the day on November 7, 2008 with Paula Rinaldi; however this information was not communicated to Drs.

Hukkelhoven or Orloff. Drs. Hukkelhoven and Orloff expressed their concern and desire to have the proper Novartis Staff available for the November 12, 2008 teleconference if possible findings were to be discussed. DSPTP noted Novartis's concern about not knowing the topic of the requested teleconference and provided the necessary information.

DSPTP used this opportunity to also request Novartis include at the upcoming Advisory Committee meeting a slide and discussion in their presentation of the data which supports the use of Coartem in adult patients  $\geq 70\text{kg}$ , as this population is thought to be most representative of the United States. population.

DSPTP also requested the following information be submitted to the NDA.

- An analysis of Fever Clearance Time in children, which accounts for use of antipyretics, including a discussion of the effects of antipyretics on fever in patients with malaria. This information had previously been requested to be included in the Novartis Briefing Book for the Advisory Committee meeting during the Face to Face presentation on October 15, 2008. However, the Briefing Book did not contain the information and it is still needed for review.
- Clarification on which formulation(s) of Coartem Tablets was used in Study A2401.

Novartis staff accepted and understood the rationale for the DSI requested teleconference on November 12, 2008 and indicated they would forward the requests on to their Coartem team. DSPTP indicated we would follow-up our requests today with an official facsimile request for this material.

---

Gregory DiBernardo  
Regulatory Project Manager

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/s/

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Joette Meyer  
2/25/2009 02:49:26 PM



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on September 23, 2008. The purpose of the teleconference was to discuss with Novartis Regulatory Affairs the ongoing obstacles encountered in scheduling FDA inspections at the Chinese and Thailand clinical sites, along with the inspection at Novartis Pharmaceuticals Corporation Headquarters in Basel, Switzerland.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** September 23, 2008

**APPLICATION NUMBER:** NDA 22-268

**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

### Novartis Pharmaceuticals Corporation

Susan Kummerer, M.S.	Director, Drug Regulatory Affairs
Marc Cousin, M.D.	Clinical
Anne-Claire Marrast, M.D.	Clinical
Paula Rinaldi	Drug Regulatory Affairs
Kanan Solanki	Drug Regulatory Affairs
Wayne Sadowski	Clinical Quality Assurance
Joanne Spallone	Clinical Quality Assurance
Matthew Stoudemayer	Clinical Quality Assurance

**AND:**

### Food and Drug Administration

Renata Albrecht, M.D.	Division Director, Division of Special Pathogen and Transplant Products, (DSPTP)
Joette Meyer, Pharm. D.	Acting Clinical Team Leader, DSPTP
Judit Milstein	Chief, Project Management Staff, DSPTP
Gregory DiBernardo	Regulatory Project Manager, DSPTP
June Germain	Regulatory Project Manager, DSPTP
Joseph Salewski	Deputy Director, Division of Scientific Investigation (DSI)
Tejashri Purohit-Sheth, M.D.	Branch Chief, Good Clinical Practice-2 (GCP-2), DSI
Susan Thompson, M.D.	Medical Officer, GCP-2, DSI

**SUBJECT:** DSPTP and Division of Scientific Investigation (DSI) discuss with Novartis Regulatory Affairs the ongoing obstacles to scheduling FDA inspections at Chinese and Thailand clinical sites and Novartis Headquarters

**BACKGROUND:**

Division of Special Pathogen and Transplant Products (DSPTP) requested this teleconference on behalf of the Division of Scientific Investigation (DSI) staff who had become increasingly concerned about communication and accessibility in completing foreign clinical inspections at sites in Thailand and China. DSI had been in communication with Novartis Quality Assurance staff coordinating these foreign clinical site inspections for a number of weeks through Dr. Attila Kadar (FDA, International Operations Branch,

Division of Field Investigations). However, within the last two weeks communication between Dr. Kadar and Novartis Quality Assurance staff and coordination of these site inspections seemed increasingly problematic, thus leaving Dr. Kadar with no opportunity to move this process forward. DSI, recognizing the tight timeline for this Priority NDA review, believed it imperative to communicate the concerns they and Dr. Kadar have to Novartis Regulatory Affairs staff in the hopes of finding a way to keep their goal of inspecting the requested sites in an appropriate time frame. Additionally, Dr. Kadar had expressed to DSI difficulty in gaining an agreement from Novartis Quality Assurance staff on the requested two week time frame to perform a sponsor-monitor inspection at the Novartis Headquarters in Basel, Switzerland. DSI wants Novartis to understand and accept the following points as critical to the review of NDA 22-268 and that, if not met; the approvability of NDA 22-268 would be in question.

- DSI inspectors must be allowed the requested 3 week time period to conduct inspections at 2 sites in Thailand.
- DSI inspectors the requested must be allowed the 2 week time period to conduct a site inspection at Novartis Headquarters in Basel, Switzerland.
- DSI inspectors must be allowed access to the Chinese clinical sites

Novartis indicated that the studies contained in the NDA, in some instances, are 10 years old, the death of a few of the Principal Investigators involved in studies have complicated inspection logistics, clinical records have been relocated or are relatively inaccessible, and the types of sites involved in these studies are not typical (e.g., refugee camp, military hospital). Novartis is working to contact Dr. Nosten (one of two principal investigators to be inspected in Thailand) but since he is traveling it has been difficult to assure he will be available for the three weeks requested for his site. Novartis indicated gaining access to the Chinese sites involves a two step process. The first step is Novartis has to invite the identified FDA inspector to come to the Chinese hospital as their guest. The second step, once DSI has identified its inspector, is Novartis will need the following information which will be given to the Chinese officials: a copy of the first page of the individual's passport, their age, gender, country of origin, occupation, CV, and purpose of the visit. Once all this information is given to the Chinese officials, they must approve the visit and then the inspections can occur following the FDA inspector completing all the foreign Visa paper work to come to China. Novartis did ask the Chinese officials if records could be moved off site, but the Chinese officials did not agree.

#### **SUMMARY:**

Novartis and DSI staff agreed to work together to move the inspection process forward. The following are the items both DSI and Novartis agreed to as an outcome of this teleconference:

- FDA DSI inspectors will have access to the 2 Thailand sites for 3 weeks as requested.
- FDA DSI inspectors will have access to the Novartis Headquarters for 2 weeks as requested.
- Dr. Kadar will identify an inspector(s) to complete the Chinese site inspections, hopefully by September 26, 2008.
- Novartis will extend an invitation to inspect the Chinese hospital site to the DSI inspector(s).
- Dr. Kadar will provide all the requested information to Novartis as quickly as possible to complete the process of gaining access to the Chinese clinical sites.

#### **ACTION ITEMS:**

- Novartis will send an e-mail to Dr. Kadar to confirm that the 3 week inspection of the 2 Thailand sites is acceptable, so the site inspector selection can be finalized; please copy Susan Thompson of DSI on this e-mail.
- Since Novartis agrees that a 2 week inspection of their Headquarters is acceptable, please again send an e-mail confirmation of this information to Dr. Kadar and Susan Thompson (DSI).
- Novartis will extend an invitation to the FDA inspector(s) to access the Chinese Hospital site for inspection, as the first step in the process to gain access to these facilities.
- DSI will coordinate communication with Dr. Kadar who will identify another inspector for the Chinese sites and will then, provide all requested information to Novartis Quality Assurance staff to facilitate the process of providing the identified inspector access the Chinese sites. This was the second step in the process for FDA inspectors to access the hospital site.

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Gregory DiBernardo  
Regulatory Project Manager

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/s/

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Joette Meyer

2/25/2009 02:46:57 PM



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on November 12, 2008. The purpose of the teleconference was discuss with Novartis Regulatory Affairs the concerns regarding procedures involving the inspection at Novartis Headquarters in Basel, Switzerland.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** November 12, 2008

**APPLICATION NUMBER:** NDA 22-268

**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

### Novartis Pharmaceuticals Corporation

#### **East Hanover Meeting Attendees:**

Ron Califre, M.D.	Senior Vice President Research and Development
John Orloff, M.D.	Head U.S. Medical and Drug Regulatory Affairs
Susan D'Amico	Vice President and Global Head Clinical Quality Assurance
Joanne Spallone	Executive Director Clinical Quality Assurance
Paula Rinaldi Head,	U.S. Mature Products, Drug Regulatory Affairs
Susan Kummerer, M.S.	Director, Drug Regulatory Affairs
Michael Bruckheimer	Corporate Compliance Officer, Global Quality Operations

#### **Via Teleconference Basel, Switzerland**

Heiner Gruenigner, Ph.D.	Global Program Head, Trop Med Initiatives & EGM
Anne-Claire Marrast, M.D.	Global Program Medical Director

**AND:**

### Food and Drug Administration

Renata Albrecht, M.D.	Division Director, Division of Special Pathogen and Transplant Products, (DSPTP)
Joette Meyer, Pharm. D.	Acting Clinical Team Leader, DSPTP
Judit Milstein	Chief, Project Management Staff, DSPTP
Gregory DiBernardo	Regulatory Project Manager, DSPTP
Leslie Ball, M.D.	Director, Division of Scientific Investigation, (DSI)
Joseph Salewski	Deputy Director, DSI
Tejashri Purohit-Sheth, M.D.	Branch Chief, Good Clinical Practice-2 (GCP-2), DSI
Susan Thompson, M.D.	Medical Officer, GCP-2, DSI

**SUBJECT:** Division of Special Pathogen and Transplant Products (DSPTP) and Division of Scientific Investigation (DSI) to discuss with Novartis Regulatory Affairs the concerns regarding procedures involving the inspection at Novartis Headquarters in Basel, Switzerland

### **BACKGROUND:**

Division of Special Pathogen and Transplant Products (DSPTP) requested this teleconference on behalf of our Division of Scientific Investigation (DSI) staff who had become concerned about communication with Novartis and the sequence of events which took place during a High Priority User Fee NDA pre-approval Sponsor/Monitor/CRO inspection at Novartis Headquarters in Basel, Switzerland.

**SUMMARY:**

DSI referenced a September 23, 2008 teleconference between FDA and Novartis Pharmaceuticals Corporation (Novartis) indicating there was an understanding that all sponsor records would be located at the Novartis Headquarters in Basel, Switzerland and made available to the DSI inspector at that location. However, at the time of the Novartis Headquarters' inspection, DSI was informed through the site inspector (Peter Lenahan) that all the records were not located in Basel Switzerland, specifically the original case record forms (CRFs). Again, through Mr. Lenahan, DSI was informed these records were stored at a location in Horshorn, United Kingdom.

Novartis provided the following background: Mr. Lenahan arrived at Novartis's East Hanover, New Jersey site on September 4, 2008 for a Sponsor/Monitor/CRO inspection unannounced. Mr. Lenahan was told the Coartem records were in Basel, Switzerland and Novartis could have the records shipped to New Jersey; however this action would take a few days to complete. Novartis also stated Mr. Lenahan was told at that point that although most of the records were in Basel, the CRFs were located in Horshorn, United Kingdom. Novartis also stated that they offered to have the records in Basel shipped to the United Kingdom, so all records would be in one location.

DSI stated that they were informed by Mr. Lenahan that the records were so voluminous that he felt he should go to Basel, Switzerland. They also stated it is not clear why Mr. Lenahan did not preannounce his inspection in New Jersey because his instructions were to do so, and they will discuss this issue further with the District Office. DSI stated that they were informed by Mr. Lenahan during his inspection in Switzerland that the CRFs were located in the United Kingdom.

Novartis replied that they did not state the records were so voluminous that they could not be moved from Switzerland. Instead, Novartis stated they provided Mr. Lenahan every opportunity to ask for what he required and never, at anytime, did they tell Mr. Lenahan that he could not have access to the CRFs.

The conversation then turned to a discussion regarding another NDA, not Coartem. DSI indicated they had been contacted by the New Jersey District Office regarding another NDA held by Novartis where a field inspector stated the records for that NDA were located at more than one site. Novartis acknowledged they have different campuses within the proximity of two towns in New Jersey, but stated the facilities are within two miles of each other. DSI indicated the FDA's District Office and Office of Regulatory Affairs do not expect inspectors to have to travel to several sites during an inspection. Novartis emphasized it was two sites, not several, and they offered the inspector one of two options: go to one location where the records are kept or go to the other location where the staff are located for help with questions. DSI emphasized to Novartis the need to accurately document where records are kept and that inspections are always pre-announced. DSI stated they will follow up with the District Office to let them know the topic of records being in more than one location was discussed.

Retuning to the discussion of the Coartem NDA inspections, Novartis asked when they will have closure of the Sponsor/Monitor/CRO inspection in Basel, Switzerland since the inspector did not leave a Form FDA 483. They wanted to know if Mr. Lenahan was still in Europe and whether they could expect him to deliver the Form FDA 483. DSI indicated they do not have a definitive answer to this question at the current time. Novartis asked how they should communicate with FDA regarding this issue. DSI indicated communication should come to them from Dr. Attila Kadar (FDA, International Operations Branch, Division of Field Investigations) and Dr. Kadar will follow-up with Novartis regarding the Form 483. Novartis asked if not having a Form FDA 483 would adversely affect the review, and DSI indicated the lack of a Form 483 will not affect the review.

Novartis asked if DSI could share any of the findings of the Basel, Switzerland inspection.

DSI stated they could not discuss any findings during this call. Novartis wanted to know when they could expect to hear more about any findings. DSI stated that the Form FDA 483 should contain similar information to the summary the inspector presented to Novartis during his visit.

Novartis stated they wanted to close the loop on this issue with the FDA District Office. DSI stated Mr. Lenahan and his supervisory chain at the District Office will contact Novartis.

Finally, DSI thanked Novartis for their time and input on gaining a better understanding of the events that took place during the Basel, Switzerland inspection and the discussion on an issue related to another NDA. Novartis emphasized that if there are any other concerns to please not hesitate to contact them.

**ACTION ITEMS:**

DSI stated they are not clear why inspector, Peter Lenahan, did not preannounce his inspection at the Novartis East Hanover, New Jersey site on September 4, 2008. His instructions were to preannounce this inspection in advance, and DSI will discuss this specific issue further with the District Office.

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Gregory DiBernardo  
Regulatory Project Manager

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Joette Meyer  
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NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on November 25, 2008. The purpose of the teleconference was to discuss concerns related to gaining access for Novartis foreign visitors to the December 3, 2008 Advisory Committee Meeting.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** November 25, 2008

**APPLICATION NUMBER:** NDA 22-268

**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

**Novartis Pharmaceuticals Corporation**

Paula Rinaldi

U.S. Regulatory Head, Mature Products and Tropical Medicines

**AND:**

**Food and Drug Administration**

Joette Meyer, Pharm. D.

Acting Clinical Team Leader, Division of Special Pathogen and  
Transplant Products, (DSPTP)

Gregory DiBernardo

Regulatory Project Manager, (DSPTP)

**SUBJECT:** Novartis Concerns that Foreign Staff will not be able to attend December 3, 2008 Advisory Committee Meeting

**BACKGROUND:**

NDA 22-268 has been scheduled for an Advisory Committee Meeting on December 3, 2008. U.S. Regulatory Head, Paula Rinaldi, was informed by Janie Kim of the Advisors and Consultants Staff and Sebastian Malvagna, of the FDA Physical Security Office that the foreign staff Novartis Pharmaceuticals Corporation (Novartis) plan to bring to the Advisory Committee Meeting may not be cleared by FDA Physical Security Office in time for the meeting due to the late submission of their Foreign Visitor Data Request Forms, and therefore not allowed into the building at 5630 Fishers Lane. DSPTP was informed Novartis only received these forms from Janie Kim on a few days earlier, but had completed the forms and returned them to the appropriate staff at FDA. DSPTP assured Novartis we would provide our assistance.

**SUMMARY:**

DSPTP informed Novartis that since we are now aware of this issue we will work on it and do all we can to work with the Advisors and Consultants Staff to ensure that all Novartis presenters and consultants be allowed access to the meeting. DSPTP expressed its understanding of the importance and vital need for the foreign staff to be present at the Advisory Committee Meeting on December 3, 2008.

DSPTP used this opportunity to communicate some other issues related to our review of NDA 22-268:

- To reiterate that the proposed label sent to Novartis on November 21, 2008 and discussed at the teleconference on November 25, 2008, was only an initial proposal and that DSPTP anticipated additional edits would follow after the discussion at the Advisory Committee Meeting on

December 3, 2008.

- To verify and provide an explanation for the number of pediatric patients with severe renal impairment provided to DSPTP in response to a request of November 12, 2008.
- To provide populated tables for the Clinical Studies section of the proposed label (as requested in the proposed label sent to Novartis on November 21, 2008 by tomorrow).

**Novartis asked the following questions of DSPTP:**

- Novartis wanted to know if they could see the DSPTP Background Package, Project Manager said he would follow-up.
- Novartis wanted to know if DSPTP could share its Advisory Committee slides with Novartis
- Paula Rinaldi provided the following contact information and requested to please contact her via telephone number (862) 222-3200 if DSPTP had questions.

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Gregory DiBernardo  
Regulatory Project Manager

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/s/

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Joette Meyer  
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NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on July 8, 2008. The purpose of the teleconference was to further clarify the specific types of subject records which need to be identified and inspected by Division of Scientific Investigation (DSI) at the clinical sites submitted to NDA 22-268.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** July 8, 2008  
**APPLICATION NUMBER:** NDA 22-268  
**DRUG NAME:** Coartem® Tablets  
**BETWEEN:**

### Novartis Pharmaceuticals Corporation

James L. DeMartino, Ph.D. Director, Drug Regulatory Affairs  
Wayne Sadowski Head Clinical Quality Assurance-Auditing-The Americas

**AND:**

### Food and Drug Administration

Joette Meyer, Pharm. D. Acting Clinical Team Leader, Division of Special Pathogen and  
Transplant Products, (DSPTP)  
Diana Willard Chief, Project Management Staff, DSPTP  
Gregory DiBernardo Regulatory Project Manager, DSPTP

**SUBJECT:** DSPTP to further clarify to Novartis the specific types of subject records that need to be identified at clinical sites to be inspected by Division of Scientific Investigation (DSI)

### **BACKGROUND:**

A May 9, 2008 submission from Novartis Pharmaceuticals Corporation (Novartis) contained clinical site information for the studies that had been agreed upon by Novartis and Division of Special Pathogen and Transplant Products (DSPTP) as the 8 key clinical studies for this NDA. In a June 10, 2008 e-mail communication from DSPTP to Novartis (e-mail attached below), DSPTP requested updated information on specific site and subject clinical records for some of the 8 key clinical studies. Novartis's July 1, 2008 submission to NDA 22-268 Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets contained updated information which was in response to the DSPTP's June 10, 2008 e-mail communication.

This teleconference was arranged at DSPTP's request to further clarify to Novartis the specific type of subject record documentation DSPTP clinical review team needs verified for a clinical inspection by DSI at each of the 8 key clinical study sites. Novartis submitted the final part of the NDA on June 27, 2008, since that time additional information requests developed; therefore DSPTP wanted to use this teleconference as an opportunity to request this information from Novartis.

### **SUMMARY:**

Following introductions and a brief synopsis of the background for the teleconference, DSPTP began the discussion by presenting the following points:

Noting that Novartis's July 1, 2008 submission states, "records including lab records, are available at the site," DSPTP asked Novartis to clarify if source documents, such as patient charts, are available. DSPTP specifically asked for clarification on what source documents are available for Center 3, Study 025 and for Center 2, Study 026, and for clarification of what is missing from the documents listed, since Novartis's explanation in the July 1, 2008 submission was vague in nature. Novartis stated that they will need to contact their colleagues in Switzerland to address this issue and will get back to DSPTP with an answer.

DSPTP requested the following information be submitted to the NDA:

- an integrated Table of Contents for the NDA that would include the date of the submission(s), folder name, and file name/study report (if applicable)
- product labels from foreign approvals for Coartem®/Riamet® be submitted in English
- any records of clinical site inspections from other regulatory agencies that have completed clinical site inspections at the sites for the 8 key clinical studies

Novartis stated that they will provide a comprehensive Table of Contents and product labels from foreign approvals. In addition, they agreed to determine whether there are any records of clinical site inspections from other regulatory agencies for the eight key clinical studies, and if so, submit those records to the NDA.

DSPTP asked Novartis to provide updates to two important outstanding requests, the first was a July 2, 2008, request for further justification for a Priority Review and the second a June 23, 2008, request for supportive information from the QT-IRT regarding the Thorough QT Study report submitted to NDA 22-268. Novartis indicated they would submit the Priority Review justification by the end of the week and submit all the materials for the QT-IRT request on July 9, 2008, but would provide this information as a desk copy as soon as it is available.

Novartis agreed to follow-up on these outstanding issues and to submit formal responses to the NDA. If further clarification on these submissions is needed this will be communicated to Novartis from DSPTP.

Novartis agreed to provide to DSPTP the following information:

- to clarify the records and source documentation
- to indicate what information is not available at the at designated clinical sites for the 8 key studies
- to create a integrated master Table of Contents, with submission information and date of submission for all disciplines
- to provide product labels for Coartem®/Riamet® in other languages (at least 2 more) translated to English
- to provide a desk copy of Novartis's response to DSPTP's June 23, 2008 fax for supportive information for the QT-IRT consult via e-mail when available
- to provide a date for the submission of DSPTP's July 2, 2008 facsimile for further support of Applicant's request for a Priority Review
- to provide any information from other regulatory agencies that have performed site inspections at any of the sites listed in the 8 Key Clinical Studies, this information will be provided by Mr. Sadowski through Dr. DeMartino

It was established in a separate telephone conversation on July 14, 2008 between Dr. DeMartino and Mr. DiBernardo that the action items listed above would be submitted to the DSPTP on or around July 21, 2008.

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Gregory DiBernardo  
Regulatory Project Manager

**E-mail sent to Novartis on June 10, 2008:**

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**From:** DiBernardo, Gregory  
**Sent:** Tuesday, June 10, 2008 4:19 PM  
**To:** 'james.demartino@novartis.com'  
**Cc:** Willard, Diana M  
**Subject:** NDA 22-268-Coartem-Novartis-8 Key study updates

Hello Jim,

Thank you for responding to my telephone message earlier. I was speaking with some of our clinical review team and a couple questions came up. I wanted to know if you could provide some updates? Your submission dated May 9, 2008 contained clinical site information for the 8 key clinical studies. We would like to know if you have any updated information on all of these sites that addresses the missing records or records not available/located at the time of this May 9, 2008 submission?

**Study number 025**

Submission states Center number 01: PI deceased, site was attempting to locate records. Please provide update if records have been located since the May 9th submission. For Center number 03 table states PI records sent records to Novartis, but Novartis is not in possession of the records. Have these records been found/located at Novartis since this submission?

**Study number 026**

For Center number 01 the table states, the PI is deceased and that the site is attempting to locate records. Has the site located the records since the May 9th submission? For Center number 02 we would like clarification on what study documents are missing and what study documents are at this site? Are subject source documents available? Also does this site have laboratory manuals/records and patient laboratory values on site?

**Study number 028**

For Center number 01 it states PI is deceased, site is attempting to locate records. Have any of these records been located since the May 9th submission?

**Study number 2401**

For Center numbers 016, 046, and 048 it states site has not responded to status of records. Please provide update on the status of records at these sites since your May 9th submission.

**Study number 2403**

For Centers 01 and 03 submission states site working to confirm location of all records. Please provide an update on the status of records at these sites since your May 9th submission

**Study number 2303 and Study number ABMO2**

For all sites are site laboratory manuals and patient laboratory values on site? If not how far are records from site?

**For all Centers in all 8 key studies, are patient laboratory records and laboratory manuals/ records on site or not on site? If not on site, then how far are records from site?**

Thank you for your help,

Gregory F. DiBernardo  
Regulatory Project Manager  
Division of Special Pathogen and Transplant Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 6189  
Silver Spring, MD 20993  
Telephone: (301) 796-4063

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/s/

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Joette Meyer  
2/25/2009 02:54:32 PM



NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on July 28, 2008. The purpose of the teleconference was to follow up on a previous teleconference to clarify the materials to be submitted for determination of a Priority Review Classification for NDA 22-268.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** July 28, 2008  
**APPLICATION NUMBER:** NDA 22-268  
**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

**Novartis Pharmaceuticals Corporation**

James L. DeMartino, Ph. D. Director, Drug Regulatory Affairs/Novartis Pharmaceuticals

**AND:**

**Food and Drug Administration**

Joette Meyer, Pharm. D. Acting Clinical Team Leader, Division of Special Pathogen and Transplant Products (DSPTP)  
Gregory DiBernardo Regulatory Project Manager, DSPTP

**SUBJECT:** Priority Review Teleconference Follow Up

**BACKGROUND:**

On June 19, 2008, Novartis Pharmaceuticals Corporation (Novartis) submitted their justification for a Priority Review classification, DSPTP responded to this submission in a July 2, 2008 facsimile (fax) requesting additional information to address the assertion that Coartem® provides a significant improvement compared to marketed products. Novartis submitted a response to the July 2, 2008 fax on July 17, 2008; however, DSPTP agreed the submission did not provide a persuasive argument for a Priority Review classification based on our Priority Review MaPP. A July 25, 2008 teleconference between Novartis and DSPTP was held to clarify what Novartis needed to submit in a request for a Priority Review classification. Dr. Meyer requested this teleconference to further emphasize to Novartis the type of quantitative data that should go into Novartis's request for a Priority Review classification.

**SUMMARY:**

- Dr. Meyer stated there were certain endpoints that were being emphasized within the NDA submission and that if Novartis could utilize these endpoints it may strengthen their argument for a Priority Review classification. For example, showing a reduced time to fever clearance in pediatric patients over comparator and correlate it with parasite clearance time.

DSPTP then asked Dr. DeMartino if he could provide any updates on the clinical site information which had been previously requested. He said Novartis was in the process of updating their submission for Dr. Nosten's clinical site and this information should be submitted to the NDA tomorrow. He stated Novartis is planning to contract a Clinical Research Organization (CRO) to go to the clinical sites and examine what is physically at the sites, but this may not occur until the end of August 2008. DSPTP requested the information about contracting a CRO to investigate what is physically at the clinical sites be stated in the submission letter. Dr. DeMartino agreed it would be done.

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Gregory DiBernardo  
Regulatory Project Manager

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Joette Meyer  
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NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on August 13, 2008. The purpose of the teleconference was to discuss the Division of Special Pathogen and Transplant Products concerns with the following: information requests being delayed, incomplete submissions to the NDA, and general management of NDA 22-268.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** August 13, 2008  
**APPLICATION NUMBER:** NDA 22-268  
**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

**Novartis Pharmaceuticals Corporation**

John Cutt	U.S. Director, Drug Regulatory Affairs
Paula Rinaldi	Global Brand Regulatory Director
Susan Kummerer, M.S.	Director, Drug Regulatory Affairs

**AND:**

**Food and Drug Administration**

Renata Albrecht, M.D.	Division Director, Division of Special Pathogen and Transplant Products, (DSPTP)
Joette Meyer, Pharm. D.	Acting Clinical Team Leader, DSPTP
Judit Milstein	Chief Project Management Staff, DSPTP
Gregory DiBernardo	Regulatory Project Manager, DSPTP

**SUBJECT:** Discussion on DSPTP's Concerns with Information Requests being Delayed, Incomplete Submissions, and Applicant NDA management

**BACKGROUND:**

Due to concerns DSPTP had identified over recent weeks regarding excessive time delays in submissions, incomplete submissions, and the need for DSPTP to undertake frequent follow-up on outstanding information requests, it was necessary for DSPTP to speak with Novartis Pharmaceuticals Corporation (Novartis). DSPTP understood that due to a change in the management of NDA 22-268 at Novartis from Dr. DeMartino to Susan Kummerer there may be a period of transition when requests for information may not be completed on time. However, in DSPTP's opinion there were too many delays and a breakdown in communication was occurring. Prior to the teleconference on August 12, 2008, a telephone call was placed to Mathias Hukkelhoven, Ph.D., Senior Vice President, Global Head, Drug Regulatory Affairs at Novartis to highlight DSPTP's concerns. This concern peaked when they learned Susan Kummerer would be absent from the project for two consecutive weeks and her replacement's contact information was not clearly identified to Mr. DiBernardo.

**SUMMARY:**

DSPTP emphasized its concerns that requests were being submitted to the NDA incompletely and these actions only made the NDA review more challenging. DSPTP stressed that when materials arrive in this manner more energy from DSPTP must be used to follow-up and track the remaining materials that are outstanding; this process takes away valuable time from the review team to examine submissions. DSPTP explained that when a request for information is being submitted all attempts should be made so that the request is submitted completely, not in a piecemeal manner. Since Ms. Kummerer would be

temporarily away from the project, DSPTP highlighted the importance that Ms. Kummerer's temporary replacement is identified quickly and all of her backup's contact information be provided to Mr. DiBernardo; subsequently if the backup is unavailable a second backup should be identified as a point of contact. DSPTP stressed due to the nature of this review that Ms. Kummerer or her temporary replacement should be available at all times during normal business hours and if someone is not available immediately, then DSPTP can expect to be contacted within a couple hours, not days. Novartis agreed they understood DSPTP's concerns and offered a few suggestions to assist in making the communication process better, for instance:

- When communicating by e-mail, using an alert or significant title in the Subject line, will indicate to Novartis staff that a pressing concern exists and a reply to DSPTP is needed, this will be helpful when staff are in meetings and can only view the Subject line of e-mails on their Blackberry phone.
- Novartis staff offered to provide the Project Manager an Excel spreadsheet similar to one used in-house to track the status of DSPTP requests.
- Novartis expressed a desire to work with DSPTP in trying to make the transition in management of the NDA better. In order to ensure the overall NDA review is productive for DSPTP, they stated more Novartis staff would be devoted to this project.
- Novartis indicated they would provide additional cell phone numbers, like a personal cell phone number, as an additional layer of contact information for critical requests.

DSPTP used this opportunity to ask if Novartis would provide an update on the status of a July 29, 2008 microbiology facsimile request and an August 7, 2008 clinical facsimile request. The Novartis indicated they expected to submit the microbiology response the day after the Labor Day holiday because the necessary personnel required to answer this request is currently unavailable; however they did state they expected to submit the clinical response at the end of next week.

Again utilizing this direct opportunity to speak to Novartis, DSPTP bridged the topic of an Advisory Committee (AC) Background Book. Since Coartem® Tablets are a New Molecular Entity an Advisory Committee would be required under FDAAA. Therefore, DSPTP asked if Novartis would provide a draft copy of their Advisory Committee Background Book and also asked if Novartis would travel to FDA to in advance of the AC meeting for a dress rehearsal of their presentation. Novartis agreed to provide DSPTP with a Draft Background Book and would welcome the opportunity to make a presentation to DSPTP and receive feedback on their Background Book and Advisory Presentation. DSPTP said they would work to find a time for these events to occur, perhaps in September 2008.

DSPTP used the opportunity to inquire about Novartis's willingness to use Riamet as an alternative proprietary name to Coartem® for marketing in the United States. Novartis stated they were not willing, at this time, to use an alternative name or replace the name Coartem® with Riamet® even though they realized from an April 28, 2008 facsimile that the Division of Medication Error Prevention and Analysis had disapproved use of the name Coartem®.

Finally, there was a request that tables addressing the efficacy of Coartem® in mixed infections be included in their Background Book and Presentation.

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Gregory DiBernardo  
Regulatory Project Manager

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Joette Meyer  
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NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: Susan Kummerer, M.S.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on July 25, 2008. The purpose of the teleconference was to further clarify the materials to be submitted for determination of a Priority Review Classification for NDA 22-268.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Joette Meyer, Pharm. D.  
Acting Clinical Team Leader  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure – Teleconference Minutes

## MEMORANDUM OF TELECON

**DATE:** July 25, 2008

**APPLICATION NUMBER:** NDA 22-268

**DRUG NAME:** Coartem® Tablets

**BETWEEN:**

### Novartis Pharmaceuticals Corporation

James L. DeMartino, Ph.D. Director, Drug Regulatory Affairs  
Susan Kummerer, M.S. Incoming Director, Drug Regulatory Affairs

**AND:**

### Food and Drug Administration

Renata Albrecht, M.D. Division Director, Division of Special Pathogen  
and Transplant Products, (DSPTP)  
Joette Meyer, Pharm. D. Acting Clinical Team Leader, DSPTP  
Diana Willard Chief, Project Management Staff, DSPTP  
Gregory DiBernardo Regulatory Project Manager, DSPTP

**SUBJECT:** Clarification of Materials to be submitted for determination of a Priority Review  
Classification for NDA 22-268

### **BACKGROUND:**

Novartis Pharmaceuticals Corporation (Novartis) submitted on June 19, 2008 their rationale for a Priority Review classification for NDA 22-268 Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets. On July 2, 2008, in response to Novartis's June 19, 2008 submission, DSPTP requested in a facsimile transmission additional information to address Novartis's assertion that, "Coartem® provides a significant improvement in the treatment of life-threatening malaria in terms of lack of resistance and patient compliance, is highly effective, and has an acceptable safety profile," thus warranting a Priority Review classification. According to the CDER Manual of Policies and Procedures (MaPP) "Review Classification Policy: Priority (P) and Standard (S)" [MaPP 6020.3], a determination for Priority Review should be based on whether the drug product provides safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement compared to marketed products in treating, preventing, or diagnosing disease. DSPTP stated that significant improvement can be interpreted to mean the following: evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of patient compliance, or evidence of safety and effectiveness in a new subpopulation and evidence to support this justification should come from clinical trials comparing a marketed product(s) with Coartem® or from other scientifically valid information. Novartis submitted a response to the July 2, 2008 facsimile transmission (fax) on July 17, 2008. After reviewing this submission, the clinical review team requested a teleconference to clarify the request in the July 2, 2008 fax and express why the July 17, 2008 submission was not sufficient to grant a Priority Review.

**SUMMARY:**

Following introductions and a brief synopsis of the background for the teleconference, DSPTP began the discussion by stating that the July 17, 2008, submission did not provide a persuasive argument for a Priority Review classification based on our Priority Review MaPP. Novartis would need to submit documentation that Coartem® demonstrates a significant clinical benefit using a data driven justification. The statement in Novartis's July 17, 2008 submission that Coartem® is a safe and effective therapy as compared to other licensed products was not sufficient to warrant a Priority Review. Novartis again would need to provide a quantitative argument, i.e., show a statistical difference, between Coartem® and comparator in order for a Priority Review to be granted. DSPTP stressed the need to demonstrate benefit in a clinical setting by providing a quantitative argument that Coartem® is significantly better than other approved therapies when looking at clinical outcomes/endpoints. Finally, a study or a documented series of patient positive outcomes (in comparison) that shows clinical improvement over a failed treatment would be recognized by DSPTP as supportive quantitative evidence for a Priority Review classification. Novartis stated that they clearly understood DSPTP's request to provide the quantitative data needed to make a determination regarding a Priority Review Classification for this NDA. Novartis noted that they may have a need for another teleconference with DSPTP after they speak to their clinical team in Switzerland about the requested materials, and will contact the Project Manager if another teleconference is needed.

Dr. Meyer requested that Novartis submit information to the NDA that summarizes the data in patients with mixed infections.

Novartis stated that they are working to provide to DSPTP the previously requested clinical site data. An update on the timing of a submission containing the requested data will be communicated to Mr. DiBernardo next week.

Novartis agreed to provide to DSPTP the requested information by August 1, 2008 via an e-mail communication, as an unofficial copy, to the Project Manager. The official submission will be sent to the FDA Electronic Document Room via the Gateway.

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Gregory DiBernardo  
Regulatory Project Manager

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NDA 22-268

Novartis Pharmaceuticals Corporation  
Attention: James L. DeMartino, Ph.D.  
Director, Drug Regulatory Affairs  
One Health Plaza, Bldg. 405/4051  
East Hanover, NJ 07936-1080

Dear Dr. DeMartino:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Coartem (artemether 20 mg/lumefantrine 120 mg) Tablets.

We also refer to your November 15, 2007, request for fast track designation and to your October 30, 2007 request for step-wise submission of sections of a New Drug Application under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating Coartem (artemether 20 mg/lumefantrine 120 mg) Tablets for treatment of infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum* as a fast track product.

We are granting fast track designation for the following reasons:

1. Malaria is caused by infection of red cells by various species of *Plasmodium*, of which *P. falciparum* is the most virulent of the species and causes life-threatening disease. *P. falciparum* can invade red cells of all ages, thereby enabling high levels of parasitemia to develop. Untreated *P. falciparum* infection is associated with high mortality especially in non-immune individuals or in individuals with impaired immunity. An infected patient can progress from minor symptoms to severe malaria in a few hours. As parasitemia levels reach approximately 5%, the mortality rate starts to increase. *P. falciparum* may cause cerebral malaria, severe hemolytic anemia, pulmonary edema, thrombocytopenia, and cardiovascular collapse and shock. Other manifestations of severe malaria include renal failure, metabolic acidosis, and hypoglycemia.
2. There is a need for alternative therapies for patients with uncomplicated malaria. Based on published literature, Coartem is reported to have a high level of efficacy for the treatment of uncomplicated *P. falciparum* malaria and has been reported to have an acceptable safety profile. This antimalarial drug could be a useful alternative for the treatment of uncomplicated *P. falciparum* malaria in the United States, and provide an

unmet medical need, for example, in patients who do not tolerate other antimalarials, who do not respond to other antimalarials, or who have an infection with *P. falciparum* that may be resistant to other antimicrobials.

We have also reviewed your request for step-wise submission of sections of an NDA for the indication described above and have concluded that the proposed plan, described in your request, for its step-wise submission is acceptable.

If you pursue a clinical development program that does not support use of Coartem (artemether 20 mg/lumefantrine 120 mg) Tablets for treatment of infections due to *Plasmodium falciparum*, we will not review the application or accept step-wise submission of sections of an NDA under the fast track program.

If you have any questions, please call Ms. Diana Willard, Chief, Project Management Staff, at 301-796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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