DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-268

NDA APPROVAL

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 (FDCA) for Coartem (artemether 20 mg/lumefantrine 120 mg) Tablets.

We note that NDA 22-268 was submitted for the indication of treatment of malaria in patients of 5 kg bodyweight or above with acute, uncomplicated malaria due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Please note, as was described to you by Ms. Diana Willard, Chief, Project Management Staff, via telephone on April 7, 2009 NDA 22-268 will be for the indication of the treatment of acute, uncomplicated malaria infections due to *P. falciparum*. b(4)

We acknowledge receipt of your submissions dated:

September 5, 2008 (2)	October 6, 2008	November 11, 2008	December 18, 2008 (3)
September 9, 2008 (2)	October 8, 2008	November 17, 2008 (2)	December 22, 2008 (2)
September 10, 2008	October 13, 2008	November 21, 2008 (2)	February 12, 2009
September 11, 2008	October 16, 2008	November 25, 2008 (3)	February 13, 2009
September 12, 2008	October 28, 2008	December 1, 2008	February 19, 2009
September 15, 2008 (2)	October 30, 2008 (2)	December 4, 2008	March 6, 2009
September 16, 2008 (2)	October 31, 2008 (2)	December 9, 2008	March 11, 2009
September 19, 2008	November 5, 2008	December 12, 2008	March 18, 2009
October 1, 2008 (3)	November 6, 2008 (3)	December 15, 2008	March 26, 2009

This new drug application provides for the use of Coartem (artemether/lumefantrine) Tablets for the treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-268."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton, immediate container labels, and wallet blister labels that are identical to the carton, immediate container labels, and wallet blister labels submitted December 18, 2008 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-268**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

TROPICAL DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a tropical disease priority review voucher, as provided under section 524 of the FDCA. This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This priority review voucher may be transferred by you to another sponsor of a human drug application. When redeeming this priority review voucher you should refer to this letter as an official record of the voucher. If the voucher is transferred, the sponsor to whom the voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the voucher was transferred. In addition, this priority review voucher has been assigned a tracking number, *PRV* 22268. All correspondences related to this voucher should refer to this tracking number. For additional information regarding the priority review voucher, please see FDA's guidance for industry titled "Tropical Disease Priority Review Vouchers" at http://www.fda.gov/cder/guidance/index.htm.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risk of neurologic or cardiac adverse reactions, and of genotoxicity related to lumefantrine or artemether impurities; or to identify an unexpected serious risk arising from treatment failure due to drug resistance, altered metabolism of co-administered drugs, or drug-drug interactions.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to:

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^2). 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 March 26, 2009 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 March 26, 2009 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 March 26, 2009 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 [redacted] and artemether impurities [redacted]

Lumefantrine impurities [redacted] and artemether impurities [redacted] 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 March 26, 2009 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 [redacted] and artemether impurities [redacted]

The structure of lumefantrine impurities [redacted] and artemether impurities [redacted] should be characterized using spectral procedures such as ^{1}H- and ^{13}C-NMR (nuclear magnetic resonance), infrared (IR), ultraviolet and mass spectroscopy. Tabulated, interpreted data for all spectra, and copies of IR and ^{1}H-NMR spectra should be submitted.

The timetable you submitted on March 26, 2009 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 CYP3A4.

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 Labelin*g (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 March 26, 2009 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 Labelin*g for details on the conduct of the *in vitro* study.

The timetable you submitted on March 26, 2009 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 Labelin*g for details on the conduct of the *in vitro* study.

The timetable you submitted on March 26, 2009 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 Labelin*g for details on the conduct of the *in vitro* study.

The timetable you submitted on March 26, 2009 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 March 26, 2009 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 March 26, 2009 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 March 26, 2009 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 March 26, 2009 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 March 26, 2009 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

Submit the protocols to an IND with a cross-reference letter to NDA 22-268. [redacted]

Submit all final report(s) to your NDA 22-268. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing requirements as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

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

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

POSTMARKETING COMMITMENTS

We remind you of your postmarketing commitment in your submission dated March 26, 2009. This commitment is listed below.

15. Develop a dissolution test method for Coartem Tablets to achieve a minimum [redacted] dissolution of each component, artemether and lumefantrine.

Develop a test method to achieve [redacted] 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 you submitted on March 26, 2009 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

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

MEDWATCH-TO-MANUFACTURER PROGRAM

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

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

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Edward Cox
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