DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-268/S-001 **SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation
Attention: Kanan Solanki, Pharm.D.
Manager, Drug Regulatory Affairs
One Health Plaza, Bldg. 405
East Hanover, NJ 07936-1080

Dear Dr. Solanki:

Please refer to your supplemental new drug application dated and received August 17, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Coartem® (artemether 20 mg/lumefantrine 120 mg) Tablets.

We acknowledge receipt of your submission dated February 9, 2010.

This Prior Approval supplemental new drug application provides for revisions to the Coartem labeling to update pharmacokinetic information.

This supplemental application provides for the following revisions to the package insert for Coartem®: (~~strikethrough~~ = deleted information and underlined = added information)

1. Under **HIGHLIGHTS OF PRESCRIBING INFORMATION**

   RECENT MAJOR CHANGES
   Dosage and Administration (2.4) 02/2010

2. Under **2.4 Dosage in Patients with Hepatic or Renal Impairment**

   No specific pharmacokinetic studies have been carried out in patients with hepatic or renal impairment. Most patients with acute malaria present with some degree of related hepatic and/or renal impairment. In clinical studies, the adverse event profile did not differ in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. No specific dose adjustments are needed for patients with mild or moderate hepatic impairment.

   In clinical studies, the adverse event profile did not differ in patients with mild or moderate renal impairment compared to patients with normal renal function. There were few patients with severe renal impairment in clinical studies. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin (DHA) in healthy volunteers and while clinical experience in this population is limited, no dose adjustment

is recommended. ~~No specific dose adjustments are needed for patients with mild to moderate renal impairment.~~

3. Under **8.6 Hepatic and Renal Impairment**

   No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. Coartem Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and DHA, no dose adjustment for the use of Coartem in patients with renal impairment is advised. No dosage adjustment is necessary in patients with mild to moderate hepatic ~~and/or renal~~ impairment. [*see Dosage and Administration (2.4)* and *Warnings and Precautions (5.6)*].

4. Under **12.3 Pharmacokinetics**

   Elimination

   Artemether and DHA are cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated more slowly, with a terminal half-life of 3-6 days in healthy volunteers and in patients with *falciparum* malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether and lumefantrine.

   ~~No urinary excretion data are available for humans.~~ In 16 healthy volunteers, neither lumefantrine nor artemether was found in the urine after administration of Coartem, and urinary excretion of DHA amounted to less than 0.01% of the artemether dose. ~~In animal studies, artemether metabolites were largely excreted in the urine. However, urinary excretion of artemether, lumefantrine and lumefantrine metabolites was negligible. While animal data are informative, they do not always predict human results.~~

   Hepatic and Renal Impairment

   No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. There is no significant renal excretion of lumefantrine, artemether and DHA in healthy volunteers and while clinical experience in this population is limited, no dose adjustment in renal impairment is recommended [*see Dosage and Administration (2.4)*].

5. Under **HOW SUPPLIED/STORAGE AND HANDLING**

   ~~Unit dose carton of 24 tablets (4 x 6-tablet blister cards) NDC 0078-0568-43~~

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)(1)(i)] 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 and text for the patient package insert). For administrative purposes, please designate this submission, **"SPL for approved NDA 22-268/S-001."**

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
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

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

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

Enclosure: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22268	SUPPL-1	NOVARTIS PHARMACEUTICALS CORP	COARTEM

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

/s/

RENATA ALBRECHT
02/17/2010