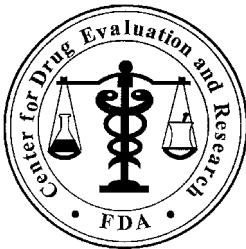


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-268

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 23, 2008

To: Renata Albrecht, MD
Director, Division of Special Pathogens and Transplant Products

Through: Todd Bridges, RPh, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Coartem (Artemether and Lumefantrine) Tablets
20 mg/120 mg

Application Type/Number: NDA# 22-268 (IND# 75,287)

Applicant: Novartis Pharmaceuticals Corporation

OSE RCM #: 2008-1280

1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Coartem (OSE RCM #2008-1280) on November 7, 2008 in which we made recommendations regarding the proposed container labels, carton and insert labeling. Subsequently, the Applicant submitted their revisions addressing DMEPA's requested changes on December 18, 2008. This memorandum is written in response to these revisions.

2 MATERIAL REVIEWED

DMEPA reviewed our initial labeling review for Coartem signed on November 7, 2008 in OSE RCM #2008-1280 and we also reviewed the revised labels and labeling forwarded to DMEPA from the review Division by e-mail dated December 18, 2008 (container labels and carton labeling) and

December 19, 2008 (insert labeling). See Appendices A through D for images of the labels and labeling.

- Container Label – 24 count bottle, 6 tablet blister label and card (Appendices A through C)
- Carton Labeling for 4 x 6 tablet blister cards (Appendix D)
- Package Insert Labeling (no image)

3 DISCUSSION

The Applicant has changed the labels and labeling according to our recommendations and we have no further comments.

4 CONCLUSIONS AND RECOMMENDATIONS

The Applicant has satisfactorily revised the labels and labeling per our November 2008 request.

If you have any questions or need clarifications, please contact Darrell Jenkins, OSE Project Manager, at (301) 796-0558.

3 pages after this page of draft labeling has been withheld as b4 (CCI/TS).

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

/s/

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12/22/2008 05:10:40 PM
DRUG SAFETY OFFICE REVIEWER

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MATERNAL HEALTH TEAM (MHT) REVIEW

Date: 11-14-2008 **Date Consulted:** 8-20-2008

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team

Through: Karen B. Feibus, M.D.
Medical Team Leader, Maternal Health Team

Through: Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Special Pathogens and Transplant Products (DSPTP)

Drug: Coartem (artemether/lumefantrine) NDA 22-268

Sponsor: Novartis Pharmaceuticals Corporation

Subject: Pregnancy Labeling and Pregnancy Registry Data

Materials Reviewed: Sponsor's submissions: proposed label, Pregnancy Registry Report, cumulative safety report, 120 safety report; Pubmed, Reprotox, TERIS, CDC Guidelines for the treatment of malaria, WHO Guidelines for the treatment of malaria

Consult Question: 1. Review the sponsor's (b) (4)

- 2. Review proposed pregnancy labeling
- 3. Review the Pregnancy Registry data

EXECUTIVE SUMMARY

Coartem, a combination of artemether and lumefantrine, is an antimalarial drug currently marketed outside the United States. In their NDA submission (N 22-268), the sponsor proposes (b) (4) and be assigned a Pregnancy Category C (b) (4)

They base this recommendation on published reproductive toxicology data regarding other artemisinin derivatives, which show cardiovascular and musculoskeletal deformities in animal offspring. The Division of Special Pathogens and Transplant Products (DSPTP) consulted the Maternal Health Team (MHT) for a review of submitted data on use of Coartem in pregnant women and labeling recommendations.

Coartem's reproductive toxicology studies are negative except for a high rate of embryo-fetal loss in rats and rabbits that is significantly elevated over background rates. Published reproductive toxicology data on lumefantrine alone are negative.

The sponsor conducted a prospective pregnancy registry in Zambia in collaboration with the World Health Organization (WHO) from October 2004 to August 2007. The registry compared pregnancy outcomes of 495 women exposed to Coartem with those of 501 women exposed to sulfadoxine and pyrimethamine (SP), which is the standard of care for treatment of malaria in pregnant women in Zambia. There were 144 exposures to Coartem in the first trimester of pregnancy. The results show no difference between exposure groups in rates of spontaneous abortion, preterm delivery, low birth weight, perinatal mortality, or neonatal mortality. The incidence of birth defects was low in both exposure groups. Although data from this cohort study have limitations due to study design, access to care, and cultural traditions, the data collected still provide important information regarding pregnancy exposure. Published findings on more than one thousand pregnancies exposed to artemisinin derivatives are consistent with outcomes from the registry.

MHT recommends that (b) (4) based on: cumulative human safety data, which do not show an increased risk for major malformations overall or increased rates of spontaneous abortion; potential clinical benefit and animal reproductive toxicology studies that show only increased embryo-fetal loss. Based on regulatory definitions of the pregnancy categories, Coartem should be assigned a Pregnancy Category C due to the increase in embryo-fetal loss in animal studies.

MHT recognizes that resource limitations exist in the countries where antimalarial studies occur. In order to address some of the limitations of the pregnancy registry, and continue ongoing pregnancy surveillance, the sponsor should consider establishing an international antimalarial pregnancy exposure registry, perhaps in collaboration with other antimalarial drug developers, and international agencies like the WHO. Please see the list of recommendations at the end of this review regarding submission of the final pregnancy registry report and post-marketing requirements regarding lactation and pharmacokinetic studies in pregnant women.

INTRODUCTION

On June 27, 2008, Novartis Pharmaceuticals Corporation submitted an NDA for priority review to the Division of Special Pathogens and Transplant Products (DSPTP), for the treatment of malaria in patients weighing 5 kg or more with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Coartem is effective against both drug-sensitive and drug-resistant *P. falciparum* and is recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials. This application included the preliminary report from a Pregnancy Registry conducted in Zambia that compares pregnancy outcomes of women exposed to Coartem with those of women exposed to sulfadoxine and pyrimethamine (SP), the standard of care for treatment of malaria in pregnant women in Zambia. The DSPTP consulted the Maternal Health Team (MHT) to review the Pregnancy Registry results, the sponsor's^{(b)(4)}

This review summarizes Coartem's cumulative pregnancy safety data and discusses the rationale for the MHT's response to the sponsor's proposal^{(b)(4)}

BACKGROUND

Overview of malaria and pregnancy

Malaria is caused by a protozoan parasite within erythrocytes and is transmitted in nature from person to person by the bite of an anopheles mosquito vector. Four principal plasmodium species cause human malaria: *Plasmodium falciparum* (which is potentially fatal), *P. vivax*, *P. ovale*, and *P. malariae*. Of the approximately 1,500 imported cases of malaria reported annually in the United States, almost two thirds are due to *P. falciparum*¹. Malaria continues to be one of the most important and devastating infectious diseases in developing areas of the world. Worldwide, over 40% of the population lives in areas where malaria transmission occurs (i.e., parts of Africa, Asia, the Middle East, Central and South America, Hispaniola, and Oceania)². It is estimated that 300-500 million cases of malaria occur each year resulting in 750,000-2 million deaths³. Malaria infection is more severe in pregnancy and is associated with higher risks of spontaneous abortion, stillbirth, preterm delivery, intrauterine growth restriction, and congenital infection⁴. In Sub Sahara Africa, approximately 25 million pregnant women are at risk of *Plasmodium falciparum* infection every year, and one in four women have evidence of placental infection at the time of delivery⁵. The Centers for Disease Control and Prevention (CDC) recommends chloroquine treatment for pregnant women with malaria. However, due to extensive resistance to chloroquine, quinine and clindamycin⁶ are recommended in the treatment of pregnant women diagnosed with chloroquine-resistant *P. falciparum*. The World Health Organization (WHO) recommends quinine and clindamycin for seven days in the first trimester

¹ Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance -- United States, 2006. MMWR Surveill Summ 2008;57:24-39

² World malaria situation in 1994. Part I. Population at risk. Wkly Epidemiol Rec, 1997. 72(36): p. 269-74.

³ Breman, J.G., The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. Am J Trop Med Hyg, 2001. 64(1-2 Suppl): p. 1-11.

⁴ Griffith KS, et al. Treatment of malaria in the United States-A systematic review. JAMA 2007;297:2264-77.

⁵ Desai M, et al. Epidemiology and burden of malaria in pregnancy. 2007 Lancet Infect Dis;7:93-104.

⁶ CDC Treatment guidelines for malaria March 2007

of pregnancy. Artemisinin combination therapy can be used if it is the only treatment available⁷. In the second and third trimesters, the WHO recommends quinidine and clindamycin, artemisinin combination therapy, or artesunate and clindamycin.

Published data demonstrated that prevention of malaria improves maternal/fetal outcomes. A meta-analysis of antimalarial prophylaxis trials or trials with intermittent preventive treatment (IPT)⁸ showed that successful prevention of malaria reduces maternal and fetal morbidity and mortality, hence the use of SP as IPT in many African countries.

Overview of Study Drugs

Coartem (artemether/lumefantrine) is a fixed combination of two antimalarials that has been marketed internationally since 1998. Both components of Coartem are blood schizontocides. Each Coartem tablet contains 20 mg of artemether (an artemisinin derivative) and 120 mg lumefantrine. Coartem is administered over three days for a total of six doses: an initial dose, a second dose after 8 hours and then twice daily (morning and evening) for the following two days. The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where the drugs are thought to interfere with conversion of heme (a toxic intermediate produced during hemoglobin breakdown) to hemozoin, the non-toxic malaria pigment. Lumefantrine is thought to interfere with the polymerization process, while artemether generates reactive metabolites through an interaction between its peroxide bridge and heme iron. Both artemether and lumefantrine secondarily inhibit nucleic acid and protein synthesis within the malarial parasite. Artemether and lumefantrine are active against the erythrocytic and gametocyte stages of Plasmodium. Thus far, there is no clinical resistance to artemether/lumefantrine, even in areas where multidrug-resistant isolates predominate.

The fixed drug combination SP (trade name Fansidar) was approved by FDA in 1981 and is indicated for treatment of acute, uncomplicated P. falciparum malaria in patients with suspected chloroquine resistance. Sulfadoxine and pyrimethamine are both folic acid antagonists. Sulfadoxine inhibits the activity of dihydropteroate synthase, whereas pyrimethamine inhibits dihydrofolate reductase. Sulfadoxine and pyrimethamine are active against the asexual erythrocytic stages of Plasmodium falciparum. Due to teratogenicity in preclinical rat studies, SP is labeled with pregnancy category C. SP has a box warning due to fatalities associated with Stevens-Johnson syndrome and toxic epidermal necrolysis and therefore, CDC does not recommend its use. Despite these rare yet severe toxicities, case reports and series of more than 1,000 pregnant women exposed to SP have not shown any adverse pregnancy outcomes^{9,10,11,12,13,14,15,16,17,18}.

⁷ WHO Guidelines for the treatment of malaria. 2006

⁸ Garner P, Gulmezoglu AM. Drugs for preventing malaria in pregnant women. *Cochrane Database Syst Rev* 2006; 4: CD000169

⁹ Barbosa JC, Ferreira I: Sulfadoxine-pyrimethamine (Fansidar) in pregnant women with Toxoplasma antibody titres. In: Siegenthaler W, Luthy R (eds). Current Chemotherapy (Proc X Int Congr Chemother Volume 1). Washington, DC: Amer Soc for Microbiol, 1978, pp 134-135

¹⁰ Couvreur J, Thulliez Ph, Daffos F, et al.: In utero treatment of toxoplasmic fetopathy with the combination pyrimethamine-sulfadiazine. *Fetal Diagn Ther* 8:45-50, 1993.

¹¹ Daffos F, Forestier F, Capella-Pavlovsky M, et al.: Prenatal management of 746 pregnancies at risk for congenital toxoplasmosis. *N Engl J Med* 318:271-275, 1988.

¹² Schultz LJ, Steketee RW, Macheso A, et al.: The efficacy of antimalarial regimens containing sulfadoxine-

Strains of *P. falciparum* with decreased susceptibility to sulfadoxine and /or pyrimethamine can be selected in vitro or in vivo. *P. falciparum* malaria that is clinically resistant to SP occurs frequently in parts of Southeast Asia and South America and is also prevalent in East and Central Africa. For these reasons, WHO recommended discontinuing its use in 2001. Also, SP may not be effective for treatment of recrudescent malaria that develops after prior therapy (or prophylaxis) with SP. The dose is 500 mg sulfadoxine and 25 mg pyrimethamine; 2 to 3 tablets as a single dose.

REVIEW OF DATA

1. Sponsor's proposed ^{(b) (4)} pregnancy label

The sponsor proposes ^{(b) (4)}

[REDACTED], based on published reproductive toxicology data regarding other artemisinin derivatives, which showed increased cardiovascular and musculoskeletal deformities in offspring.

The following is the sponsor's proposed pregnancy section of the Coartem label:

8.1 Pregnancy

^{(b) (4)}

pyrimethamine and/or chloroquine in preventing peripheral and placental *Plasmodium falciparum* infection among pregnant women in Malawi. Am J Trop Med Hyg 51(5):515-522, 1994.

¹³ Sowunmi A, Akinede JA, Omitwoju GO, et al.: Intramuscular sulfadoxine-pyrimethamine in uncomplicated chloroquine-resistant *falciparum* malaria during pregnancy. Trans R Soc Trop Med 87:472, 1993.

¹⁴ Parise ME, Ayisi JG, Nahlen BL et al: Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. Am J Trop Med Hyg 59(5):813-822, 1998.

¹⁵ Verhoeff FH, Brabin BJ, Chimsuku L et al: An evaluation of the effects of intermittent sulfadoxine-pyrimethamine treatment in pregnancy on parasite clearance and risk of low birthweight in rural Malawi. Ann Trop Med Parasitol 92(2):141-150, 1998.

¹⁶ Shulman CE, Dorman EK, Cutts F, Kauondo K, Bulmer JN, Peshu N, Marsh K: Intermittent sulphadoxine-pyrimethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomised placebo-controlled trial. Lancet 1999;353:632-6.

¹⁷ Deen JL, von Seidlein L, Pinder M et al: The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. Trans R Soc Trop Med Hyg 95:424-428, 2001.

¹⁸ van Eijk AM, Ayisi JG, ter Kuile FO et al: Effectiveness of intermittent preventive treatment with sulphadoxine-pyrimethamine for control of malaria in pregnancy in western Kenya: a hospital-based study. Trop Med Int Health 2004;9:351-60.

(b) (4)



(b) (4)



(b) (4)



MHT Discussion

Coartem's reproductive toxicology studies are negative except for an increase in pre and/or post-implantation loss, early resorptions, and abortions in rats and rabbits. Published reproductive toxicology data on lumefantrine are negative. FDA's pharmacology/toxicology reviews state that pharmacokinetic analyses in animal studies demonstrate that plasma artemether levels are sporadic and not consistently dose-related. Artemether has a complex metabolic profile that appears similar among animal models and humans, but the profiles are not identical. Nonclinical studies have not identified which artemether-related compounds are embryotoxic. Therefore, they conclude that they are unable to compare directly a safe level of artemether in animal studies to clinical human exposures. The absence of more specific embryotoxic mechanistic information limits the quantitative predictivity of the animal study findings. Please see the reproductive toxicology review of Dr. Owen McMaster for further details.

Artemisinins' embryo-toxic mechanism is thought to occur through depletion of embryonic erythroblasts (primitive erythrocytes), which is associated with severe anemia leading to cell damage and death due to hypoxia¹⁹. In humans, the most sensitive time window may be between gestational weeks four and ten, when erythroblasts circulate and have not yet been fully replaced by definitive erythrocytes²⁰. In addition to the window of sensitivity, the duration of exposure is also important. Rodents have a synchronous clonal expansion of metabolically active erythroblasts, making them particularly vulnerable during a three- to four-day window early in pregnancy. In primates (and it is also thought that most likely also in humans), this may not be the case, as different generations of erythroblasts co-exist and are progressively replaced by definitive erythrocytes over a period of weeks¹⁹. In cynomolgus monkeys, no embryo lethality or malformations were observed with three-day exposures (the typical duration of treatment with ACTs) or with seven-day exposures^{19,20,21,22}. The predictive value of the animal

¹⁹ World Health Organization (2007) Assessment of the safety of artemisinin compounds in pregnancy: Report of two joint informal consultations convened in 2006. WHO/CDS/MAL/2003.1094.

www.who.int/tdr/publications/publications/pdf/artemisinin_compounds_pregnancy.pdf.

²⁰ White TEK, Clark RL (2008) Sensitive periods for developmental toxicity of orally administered artesunate in the rat. Birth Defects Res B Dev Reprod Toxicol. E-pub 9 July 2008.

²¹ Clark R, Kumemura M, Makori N, Nakata Y, Bernard F, et al. (2006) Artesunate: Developmental toxicity in monkeys [abstract]. 46th Annual Meeting of the Teratology Society; 24-29 June 2006; Tucson, Arizona

models for humans is unclear, particularly because the duration of daily exposure is likely to be short.

The World Health Organization (WHO) now recommends the use of artemisinin combination therapies (ACTs) in the second and third trimesters of pregnancy. Due to uncertainty about their safety in early pregnancy, WHO recommends ACTs in the first trimester only when alternatives are not available. Estimates suggest that over 70% of malaria episodes in rural Africa and about 50% in urban areas are self-treated without consulting trained professionals²³. Thus, many of these will be presumptive treatments without involvement of the formal health services, diagnostic confirmation of malaria, or screening for potential pregnancy. A recent publication created a model using background statistics to predict that in Sub Saharan Africa, a woman's chance of inadvertent exposure to artemisinins during embryogenesis is 2.5%²⁴.

Please see MHT's discussion of Pregnancy Labeling recommendations on page 17 of this review.

2. Pregnancy Registry Data

Overview of Coartem Pregnancy Registry

The sponsor conducted a multicenter prospective pregnancy registry in Zambia in collaboration with the World Health Organization (WHO) and the government of Zambia, from October 15, 2004 to August 27, 2007 (date of last delivery plus 6 weeks). The registry compared pregnancy outcomes of 495 women exposed to Coartem with those of 501 women exposed to SP, which is the standard of care for treatment of malaria in pregnant women in Zambia.

Study objectives and outcomes

Primary objective:

- Evaluate the safety of Coartem in pregnant women with symptomatic malaria by measuring the incidence of perinatal mortality (defined as death within 7 days of birth and stillbirth).

Reviewer comment

The definition used for perinatal mortality is different from the one used by the American College of Obstetricians and Gynecologists (ACOG), which includes fetal demises 20 weeks and beyond, and the death of neonates up to the first 28 days of life.

Secondary objectives :

²² Clark RL, White TE, A Clode S, Gaunt I, Winstanley P, et al. (2004) Developmental toxicity of artesunate and an artesunate combination in the rat and rabbit. Birth Defects Res B Dev Reprod Toxicol 71: 380-394.

²³ McCombie SC (1996) Treatment seeking for malaria: A review of recent research. Soc Sci Med 43: 933-945.

²⁴ Dellicour S, et al. Pregnancy Exposure Registries for Assessing Antimalarial Drug Safety in Pregnancy in Malaria-Endemic countries. 2008. PLoS Med 5(9):e187.doi10.1371/journal.pmed.0050187.

- Evaluate the safety of Coartem in pregnant women with symptomatic malaria by: measuring gestational age at delivery (estimated from last menstrual period [LMP]) and birth weight adjusted for gestational age at delivery.
- Compare the safety profile of Coartem versus SP in pregnant women with symptomatic malaria relative to perinatal mortality, gestational age at delivery, and birth weight adjusted for gestational age at delivery.

Outcomes:

1. spontaneous abortion (\leq 28 weeks gestation)
2. preterm delivery ($<$ 37 completed weeks)
3. neonatal mortality (within 28 days after birth)
4. maternal mortality (up to 6 weeks following delivery)
5. birth defects
6. Neurodevelopment deficit in infants up to 12 months after birth (still ongoing, therefore are not presented in this preliminary report).

Reviewer comments

This study used definitions for spontaneous abortion and stillbirth that differ from those used in the United States. The US National Center for Health Statistic defines spontaneous abortion as embryo-fetal loss at less than 20 weeks gestation, and fetal demise as fetal death at or beyond 20 weeks gestation but before delivery. These differences will skew the numbers, thus affecting the calculated perinatal mortality rate, and may be difficult to extrapolate to U.S. populations.

Study Design

Patients were assigned to the exposure groups based on the antimalarial treatment they received for treatment of their most recent malaria episode prior to registry entry (index episode).

Subjects were assessed at each of seven visits to antenatal clinics, and mothers were followed until six weeks after birth and babies until 12 months after birth. Field workers or study nurses conducted home visits with those patients who did not attend the antenatal clinics at the time of scheduled study visit(s). It was assumed that Coartem treatment was given for 3 days and SP as a single dose. Use of antimalarial treatment was documented based on patient report. Pregnant women could also have been exposed to multiple antimalarial regimens during the course of the pregnancy, including IPT with SP, as it is standard for pregnant women in Zambia to receive IPT during the second and third trimester.

Placental biopsies were taken from 100 patients following delivery, at two sites in Choma district to verify the presence of the malarial parasite in the placenta. Results will be reported in the final report.

A Study Advisory Committee (SAC) regularly reviewed the classification of individual outcomes and accumulated registry data and provided recommendations on potential study modifications and on clinical considerations.

Sample size and power consideration

According to the sponsor, for 500 patients in the Coartem group, a two-sided 95% confidence interval for observed perinatal mortality (primary study endpoint) would vary between 3% and 7% for an assumed background incidence rate of 5% in the Zambian population. Additionally, a sample size of 500 patients in each exposure group would provide a two-sided 95% confidence interval that will vary between 1.2 and 3.3 for an observed odds ratio of 2 for perinatal mortality.

Statistical Analysis

The sponsor submitted the statistical analysis plan used to analyze the data. Statistical analysis was performed for the primary outcome, perinatal mortality only.

Results

Approximately 85% of the enrolled pregnant women participated in the registry until six weeks after delivery. In most cases, the index episode of malaria was not confirmed by microscopy or rapid diagnostic test and was based on symptomatology. Most pregnant women had only a single malaria episode, with approximately 11% having two episodes. Approximately two-thirds of patients received IPT with SP before enrollment. Treatment during the first trimester was slightly more common in the Coartem exposure group than the SP group (in 33% and 26% of patients respectively). Because of the use of IPT with SP prior to enrolment, most patients in the Coartem group had received two types of antimalarial treatment (Coartem and SP) whereas in the SP group (because IPT used SP) only SP had been used in the majority of patients, although 3.0% of patients in the SP group had also received Coartem.

Approximately 30% of patients in the Coartem exposure group and 38% in the SP exposure group were tested for HIV at registry entry – the remainder were not tested following a discussion at the clinic. In total, approximately 7% of patients in each exposure group were HIV-positive, with no notable differences between groups.

Use of common concomitant medications included a range of antibiotics and antiparasitic agents (most notably mebendazole, used in 16.6% of the Coartem group and 17.2% of the SP group), and paracetamol (acetaminophen). The latter was used more frequently by patients in the SP exposure group (26.3%) than those in the Coartem group (14.5%). Only 2.8% of patients in the Coartem group and 1.2% in the SP group reported taking anti-HIV medication (despite 7% of the population being HIV positive) and these therapies were generally triple combinations containing nevirapine, or a single agent (lamivudine, stavudine, or zidovudine).

Reviewer comments

The fact that malaria diagnosis and HIV status were not verified in most patients may confound effects of the study drug with the effects of background illness. The potential adverse event profile for pregnancy might be better for individuals who did not have malaria or HIV. The concomitant use of SP in a significant number of patients also confounds the results.

Primary outcome: perinatal mortality

Perinatal mortality was defined as stillbirths (which were defined as fetal deaths at 28 weeks and beyond) and newborn births up to 7 days of age. As shown in Table 1, there was no statistical difference between exposure groups in rates of perinatal mortality.

Table 1: Perinatal mortality statistics from Coartem pregnancy registry		
Perinatal mortality	Coartem (n=474)	SP (n=479)
n (%)	20 (4.2)	24 (5)
Asymptotic 95% confidence interval	2.4-6.0	3.1-7.0
Pearson-Clopper 95% confidence interval	2.6-6.4	3.2-7.4
Stillbirth n (%)	9 (1.9)	13 (2.7)
Neonatal death n (%)	11 (2.3)	11 (2.3)
Difference between Coartem and SP (%)	-0.8	
Asymptotic 95% confidence interval	-3.5, -1.9	
Wilson score 95% confidence interval	-3.6, -1.9	

Stillbirths

Stillbirths were defined as infants born dead at or beyond 28 weeks gestation. Stillbirths were more common in the SP group, 2.5%, vs. the Coartem group, 1.8 %. A review of the individual reports for the Coartem group stillbirths shows that out of a total of nine, one was associated with a cord accident, one was associated with prolonged labor and “fetal distress” at 44 weeks gestation, and one was associated with a febrile illness and shock.

Reviewer comments

As discussed previously, there is underreporting of the perinatal mortality rate due to classification of stillbirths as fetal deaths that occurred at 28 weeks gestation and later (rather than 20 weeks and later) and the lack of inclusion of newborn deaths up to 28 days. Recent estimates suggest that stillbirth rates of >30 per 1,000 births are common among the least developed countries, especially in Sub-Saharan Africa and Southeast Asia^{25,26}. By comparison, the stillbirth rate in the United States was 6.2 per 1,000 live births in 2003²⁷. Although the WHO attempted to standardize the definition of stillbirth by recommending 1,000 g as the lower limit for international comparisons (corresponding to approximately 28 weeks of gestation), the lower limit of the gestational age or birthweight that is reported varies widely. In developed countries, stillbirth is defined generally as fetal loss beyond 20 weeks of gestation. In the final report, the sponsor should reclassify stillbirth, and perinatal mortality according to standard US definitions, and reanalyze their data based on these definitions.

²⁵ Stanton C, Lawn JE, Rahman H, Wilczynska-Ketende K, Hill K. Stillbirth rates: delivering estimates in 190 countries. Lancet 2006;367:1487-94.

²⁶ McClure EM, Nalubamba-Phiri M, Goldenberg RL. Stillbirth in developing countries. Int J Gynaecol Obstet 2006;94:82-90.

²⁷ MacDorman MF, Hoyert DL, Martin JA, Munson ML, Hamilton BE. Fetal and perinatal mortality, United States, 2003. Natl Vital Stat Rep 2007;55(6):1-17.

The etiology of stillbirth is multifactorial, and includes causes such as congenital anomalies, chromosomal abnormalities, diabetes, Rh disease, and placental insufficiency. In Zambia, 15% of all pregnant women test positive for syphilis, and about a third of these women will have a stillbirth,²⁸ and it is, therefore, not possible to establish a cause and effect relationship between Coartem exposure and these cases. A recent study done by the NICHD First Breath Study Group showed that 66% of deliveries in Zambia occurred at home²⁹; this may account for some of the stillbirths and neonatal deaths that occurred shortly after delivery.

Although this study is a safety study, and not an efficacy study, if the background perinatal mortality rate in Zambia is in fact 5% as the sponsor states, then one would have expected a greater reduction in perinatal mortality in the treatment groups.

Neonatal deaths (up to 7 days of life)

The perinatal mortality rate included deaths of newborns up to 7 days of life and was the same in both treatment groups (2.3 %). The 11 cases of neonatal mortality up to 7 days of life in the Coartem group included four cases that are discussed in the Cumulative Safety Data section on page 15 (section 3). The remaining cases are due to either prematurity, or unknown causes.

Neonatal deaths (up to 28 days of life)

Neonatal mortality rates up to 28 days of life were identical (3.0%) in both groups. Most of the neonatal deaths occurred during the first 7 days after birth, and are included above. In the Coartem group, three additional deaths occurred between 7 and 28 days after birth: one was due to pneumonia (death occurred 9 days after birth), and in the other cases the cause of death was unknown (these deaths occurred 15 and 24 days after birth). In the SP exposure group, three deaths occurred between 7 and 28 days after birth. The cause of death in two cases (9 and 11 days after birth) was unknown; the other death, which occurred nine days after birth, was due to prematurity.

Reviewer comments

Both the US and the WHO define neonatal mortality as deaths that occur in the first 28 days of life. According to the World Health Statistics, the neonatal mortality rate in Zambia in 2000 was 4%, which is approximately ten times the US rate.

Abortions

Abortions were defined as fetal deaths that occurred up to 28 weeks gestation. Abortion rates were similar for both treatment groups (1.4% in the Coartem group vs. 1.6% in the SP group). In the Coartem group, two cases were first trimester spontaneous abortions, and four cases were second trimester fetal demises.

²⁸ Goldenberg R. Factors influencing perinatal outcomes. Ann NY Acad. Sci. 2004; 1038: 227-234.

²⁹ McClure EM, et al. The global network: a prospective study of stillbirths in developing countries. Am J Obstet Gynecol 2007;197:247.e1-247.

Reviewer comments

One case which occurred at 27 weeks gestation (ie after 20 weeks gestation) should be classified as a stillbirth. Spontaneous abortions are probably underreported, as many African cultures do not acknowledge pregnancy until after three months gestation. The study drugs are not routinely administered during the first trimester of pregnancy; however, it is not clear how accurately gestational age is confirmed at dispensing, therefore women who miscarry prior to enrollment in the study will not be captured. The study does not capture pregnancy terminations, which could provide some information regarding fetal malformations.

Birth defects

No distinction was made between minor and major malformations. The total proportion of infants with birth defects was somewhat higher in the Coartem exposure group (4.9 %) than in the SP group (2.6%); this between-group difference was almost entirely due to a higher rate of umbilical hernia in the Coartem group (3.7% vs. 1.5% in the SP group). As shown in Table 2, the other reported birth defects (except polydactyly) occurred in single patients, with no clear pattern of distribution between exposure groups, and included one case of trisomy 21.

Table 2: Summary of birth defects following Coartem exposure	
Birth Defect	Number of cases (n=23)
Umbilical hernia	17
Polydactyly	3
Trisomy 21	1
Small labia,small nose, lanugo	1
Hyperextensible joints	1

The incidence of malformations in babies born to mothers who received Coartem in the first trimester was 7.7% (9/142). Eight of the nine malformations were umbilical hernias, and the remaining baby was reported to have small labia and a small nose. Of the 17 umbilical hernias reported in the 465 babies born to mothers in the Coartem group, 8 were in babies whose mothers had used the drug in the first trimester. In the SP group, four babies born to the 124 women who received treatment in the first trimester had birth defects: two had umbilical hernias, one had malformed ears, and one had polydactyly.

Reviewer comments

Although umbilical hernias were more common in the Coartem group, it is still less than the background incidence of the study population, which has been reported to be as high as 8-23%³⁰. Polydactyly is an autosomal dominant inherited trait, and is also more common in the African population. Trisomy 21 is a genetic defect, and not likely related to drug exposure.

³⁰ Meier DE, OlaOlorun DA, Omodele RA, Nkor SK, Tarpley JL (2001)]. Incidence of umbilical hernia in African children: redefinition of "normal" and reevaluation of indications for repair. World J Surg 25: 645-648.

Birth weight

Low birth weight (adjusted for gestational age according to last menstrual period), based on standard Zimbabwean birth weight standards, occurred at similar rates in the two exposure groups (9% Coartem vs. 7.7% SP).

Reviewer comments

The reported gestational age, which was based on last menstrual period, may not be accurate, as it was not confirmed by ultrasound. Low birth weight is defined as birth weight < 2, 500 g. The reported low birth rates are similar to the US low birth weight rate, which was 8.2% in 2005, according to the National Vital Statistics Report; this may be due to the intervention.

Gestational age at delivery

Mean and median gestational age determined using last menstrual period were similar for the two exposure groups (39 and 39 weeks, respectively, for the Coartem group, and 38.9 and 39 weeks, respectively, for the SP group). Mean and median gestational age determined using the Dubowitz neurological assessment scale were very similar in both exposure groups. These values were similar to those seen when LMP was used to calculate gestational age. In the Coartem group, 0.9% of patients delivered (vs. 0.4% in the SP group) at less than 28 weeks gestation, and 12.7 % delivered between 28 and 37 weeks gestation (vs. 18.2 % in the SP group). Among Coartem treated subjects, 3.9 % of the data was missing vs. 4.7% of data for the SP group.

Reviewer comments

The reported preterm birth rate in the Coartem group is similar to the preterm birth rate in the US, which was 12.7% in 2005, according to the National Vital Statistics Report; this may be due to the intervention.

Maternal mortality

One patient in the Coartem exposure group (0.2%) and five in the SP exposure group died (1%). In the SP exposure group, one HIV-positive patient died due to Kaposi's sarcoma, three patients died due to infections (pneumonia, viral encephalitis, and sepsis), and one patient died “undiagnosed”.

The woman who died in the Coartem group was a 27 year old who had three malaria episodes during the index pregnancy. This patient had an obstetric history of two spontaneous abortions. She had no significant medical history. Concomitant medications included paracetamol for malaria as well as metronidazole benzoate and magnesium trisilicate for gastritis. By her last menstrual period (LMP), she received sulfadoxine-pyrimethamine (SP) at seven weeks gestation, and Coartem at week 10 of gestation. She entered the study after completing Coartem treatment and was found to have a hemoglobin of 10.6 g/dL one month later. At week 20, the patient was hospitalized for a severe respiratory tract infection, anemia, oral candidiasis and immunosuppression (possibly due to HIV infection but no HIV-test was performed). During hospitalization, she was treated with concentrated red blood cells for anemia, amoxicillin for

respiratory tract infection, nystatin for oral candidiasis, paracetamol, and with multivitamins as a nutritional supplement. At week 22, she had a third malaria episode treated with SP. She had a fetal demise at 22 weeks gestation and underwent uterine evacuation. At the time of her procedure, she received hydrocortisone, furosemide and dextrose. The next day the patient died due to anemia and “other underlying problems”. The investigator did not suspect a relationship between the events and the study medication.

Reviewer comments

This is a complex case with multiple confounding factors; it is therefore impossible to draw any conclusions regarding causality between the study drug and outcome. According to the World Health Statistics, the maternal mortality rate in Zambia in 2006 was 750 per 100, 000 live births, compared to 13 per 100, 000 live births in the US in 2004. The sponsor reported maternal deaths as a % of the total number of enrolled women; this should be corrected in the final report to reflect the number of maternal deaths in terms of the number of live births.

3. Sponsor’s Adverse Event Reports of Coartem Pregnancy Exposure

Coartem’s cumulative safety report included 62 prospective, and 118 retrospective pregnancy cases. The Table 3 summarizes the reported outcomes:

Table 3: Pregnancy outcomes from Coartem cumulative safety report	
Outcomes	Number
Live birth with normal fetus	85
Live birth with congenital anomaly	26
Stillbirths	9
Therapeutic abortion for fetal demise	1
Spontaneous abortion	8
Ectopic pregnancy	1
Unknown outcome	50
Total	180

The congenital malformations include 18 cases of umbilical hernia, 1 case of polydactyly, 1 case of Down’s syndrome, 1 case of physiologic patent foramen ovale, 1 case of cerebral ventricle dilation that was reported twice, 1 case of Trisomy 18, 1 case of lissencephaly, and 1 newborn reported to have an inverted left nipple with a smaller areola than the opposite side.

Reviewer comments

As discussed previously, the incidence of umbilical hernia is higher among Africans, and polydactyly is an autosomal dominant trait which is more common in Africans. Trisomy 18 and 21 are unrelated to drug use. The nipple and areola abnormality are not of clinical significance. The two brain abnormalities may be related to Coartem use; however, it is not possible to definitively establish a causal relationship.

The report includes the following four neonatal deaths, which are also included in the results of the Pregnancy Registry:

1. This is a woman who took Coartem at approximately 26 weeks gestation by last menstrual period. At approximately 31 weeks gestation, she delivered prematurely via a spontaneous vaginal delivery at a clinic. The baby was female, weighed 2 kg, and had an APGAR score of 9/10. The baby died on the same day, during transfer to the hospital.
2. This is a woman who took Coartem at approximately 6 weeks gestation by last menstrual period. At approximately 35 + weeks gestation, she delivered by herself at home. The baby was in breech presentation and died shortly after birth.
3. This is a 27 year old woman who had had a previous full term birth and a previous abortion, who took Coartem at approximately 27 weeks gestation by last menstrual period. She did not have an ultrasound or serum AFP testing during the pregnancy. She gave birth at term to a normal male neonate with a weight of 2.7 kg, and APGAR score of 9/10. At three weeks of age, the baby died at home and the cause of death was unknown.
4. This is a primigravid woman who took Coartem at approximately 10 weeks gestation by last menstrual period. She delivered at approximately 42 weeks gestation at home. The delivery and neonate were reported to have been normal. The child died two weeks later due to an unknown cause.

Reviewer comment

The death in the first case was probably due to prematurity. The death in the second case was probably due to asphyxia during breech delivery. Due to insufficient information, it is not possible to determine causality in the last two cases.

Preterm births are not reported, and the number of spontaneous abortions versus stillbirths may be inaccurate due to the definitions used, as in the Pregnancy Registry report.

In their 120 Safety Update, the sponsor submitted a case report of a congenital malformation that occurred during an investigator-initiated Coartem trial. CCOA566A2415 was a randomized controlled trial that examined the safety, tolerability and efficacy of artesunate monotherapy (AS7) with artemether-lumefantrine (AL) in pregnancy in an area of multi-drug resistance. Patients in the second and third trimesters of pregnancy with uncomplicated falciparum malaria were randomized to three days AL (n=125), or seven days of artesunate (AS7; n=128). There was one infant born following exposure to Coartem at 20 weeks gestation who had absent fingernails and toenails. There were no significant differences in the major birth indicators (e.g. estimated gestational age, proportion premature, proportion stillbirths, proportion male infants and congenital abnormality) between the groups. There was no difference in the neurological optimality score of neonates whose mothers were treated with AS7 or AL. As these are interim results, a final conclusion is not yet possible.

Reviewer comment:

It is not possible to establish a causal relationship between this one outcome and Coartem exposure. Anonychia is sometimes associated with a genetic mutation and could also arise spontaneously. Overall, there does not appear to be an increase in congenital malformations in the Coartem treatment group.

4. Data from Published Reports

The sponsor estimates that over ^{(b) (4)} patients in endemic countries have been treated with Coartem since its first introduction to market in 1998. Published findings on more than one thousand pregnancies exposed to artemisinin derivatives have not shown an increase in congenital malformations³¹. In a prospective study of 461 pregnant women exposed to artemether or artesunate, birth outcomes in terms of abortion, stillbirth, congenital malformations, or mean duration of gestation were not different from community rates³². In a study on 287 women in the Gambia who elected to receive artesunate with SP as a single dose during pregnancy, there was no increase in miscarriage, stillbirth, or fetal death in the treated group and no evidence of an increase in congenital malformation³³. A study of 83 pregnant women in Thailand treated with artemether or artesunate found no increase in adverse outcomes³⁴. Another study done in Thailand in 66 pregnant women exposed to artesunate did not show an increase in adverse birth outcomes³⁵. There are also several published case series of pregnant women who were exposed to artemisinins without any adverse pregnancy outcomes.

5. Lactation Section of Labeling

Animal studies of Coartem showed that the drugs are excreted in the milk. There are no data on the effects of Coartem during human lactation. The sponsor recommends that a woman should not breastfeed following exposure to Coartem or interrupt breastfeeding for 28 days. The WHO recommends that of all the antimalarials, including ACT's, only tetracyclines and dapsone be withheld during lactation³¹. It is not clear why the sponsor would recommend not breastfeeding to women who are exposed to Coartem, especially since it is used therapeutically in infants who weigh 5 kg and above, and since breastfeeding can be a lifesaving measure in underdeveloped countries. To assess the presence of Coartem in breastmilk and in breastfed infants, a lactation study should be conducted. The sponsor may choose to do this as a nested study, using patients who are enrolled in their pregnancy registry. For guidance on how to conduct a lactation study, the sponsor should review the Draft Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling

³¹ Guidelines for the treatment of malaria. World Health Organization 2006.

³² McGready R, Cho T, Keo NK, Thwai KL, Villegas L, Looareesuwan S, White NJ, Nosten F. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant Plasmodium falciparum. Clin Infect Dis 2001;33(12):2009-16.

³³ Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. Trans R Soc Trop Med Hyg. 2001;95:424-8.

³⁴ McGready R, Cho T, Cho JJ et al. Artemesinin derivatives in the treatment of falciparum malaria in pregnancy. Trans Roy Soc Trop Med Hygiene 1998;92:430-433.

³⁵ McGready R, Brockman A, Cho T, Cho D, van Vugt M, Luxemburger C, Chongsuphajaisiddhi T, White NJ, Nosten F. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg. 2000;94:689-93

<http://www.fda.gov/cder/guidance/5918dft.pdf>. The sponsor should submit a draft protocol for review by DSPTP and MHT within six months of product approval.

6. Pharmacokinetics in pregnancy

A study conducted in Thailand in 13 pregnant women (five in the second trimester and eight in the third trimester) with uncomplicated *P falciparum* malaria concluded that pregnancy is associated with reduced (approximately half) plasma concentrations of artemether, and lumefantrine compared to historical data in non-pregnant (1 female and 16 males) patients with malaria³⁶. All patients treated with Coartem in this study were cured despite lower exposure to artemether and lumefantrine. However, in a recent trial conducted in 103 pregnant women with falciparum malaria in the second and third trimester of pregnancy and treated with Coartem (McGready 2008, personal communication), plasma concentrations (mean [range] ng/mL) of lumefantrine (measured on day 7) were higher (483 [134-1454]) in pregnant women than those observed in non-pregnant adults (350 [204-869]) and previously reported (384 [62-835]) in study described above(McGready 2008, personal communication). There is no clear explanation for these opposite findings.

Reviewer comment

In order to clarify this discrepancy and ensure proper dosing and effective anti-malarial therapy among pregnant women, the sponsor should conduct a pharmacokinetic study in pregnant women.

7. MHT Pregnancy Labeling Recommendations and Discussion of Pregnancy Category Definitions

The sponsor proposes that^{(b) (4)}

based on published reproductive toxicology data regarding other artemisinin derivatives, which showed increased cardiovascular and musculoskeletal deformities in offspring. According to the Regulations, a Contraindication is consistent with a Category X pregnancy designation. 21 CFR 201.57 states that under Contraindications “known hazards and not theoretical possibilities shall be listed”. For guidance on the Contraindications Section of Labeling, the sponsor should review the Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format www.fda.gov/cder/guidance/5538dft.pdf.^{(b) (4)}

based on a theoretical risk of teratogenicity due to class similarity. A^{(b) (4)} is not appropriate either, as Coartem’s human data isn’t consistent with the following regulatory definition of a^{(b) (4)}

The regulation in 21 CFR 201.57 defines a Category C drug as the following: “animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the

³⁶ McGready R, Stepniewska K, Lindegardh N, et al (2006). The pharmacokinetics of artemether and lumefantrine in pregnant women with uncomplicated falciparum malaria. Eur J Clin Pharmacol; 62:1021-31.

benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, or there are no animal reproduction studies and no adequate and well-controlled studies in humans”.

Based on the fact that reproductive toxicology studies showed an increase in embryo-fetal loss, Coartem should be assigned a Category C. In terms of the limitations of the quantitative predictivity of the reproductive toxicology studies, the Reproductive and Developmental Toxicities Draft Guidance states that when exposures achieved in the animal studies may not have been adequate to fully evaluate the potential for the drug to increase the risk of reproductive or developmental toxicity in humans, the summary risk conclusion should state that the risk for adverse developmental effects in humans is unknown. This definition is consistent with Pregnancy Category C.

Please see Pregnancy Labeling recommendations on page 20 of this review

DISCUSSION AND CONCLUSIONS

Malaria infection in pregnant women is a significant global public health issue. Malaria carries a higher risk of morbidity and mortality in pregnant women than in the general population, and is associated with poor obstetrical outcomes such as spontaneous abortion, stillbirth, preterm delivery, intrauterine growth restriction, and congenital infection.

While the results of the pregnancy registry are valuable, there were some limitations based on study design limitations, limitations in access to care, and social/cultural traditions. Spontaneous abortions are probably underreported, as many African cultures do not acknowledge pregnancy until after three months gestation. The study drugs are not routinely administered during the first trimester of pregnancy; however, it is not clear how accurately gestational age is confirmed at dispensing, therefore women who miscarry prior to enrollment in the study will not be captured.

In terms of reported results, some definitions used were not consistent with standard definitions used in the U.S., and these pregnancy outcome statistics are, therefore, difficult to interpret. Although the above limitations were present in the study, MHT recognizes that despite resource limitations in the countries where antimalarial studies occur, the data collected still provide important information regarding pregnancy exposure for an American population.

The difficulty in interpreting post-marketing spontaneous adverse outcome reports is that normal outcomes do not get reported; we don't know the numerator or the denominator. The cumulative safety data from approximately 500 pregnant women exposed to Coartem in the pregnancy registry, in addition to the published data of over 1,000 pregnant women exposed to artemisinin derivatives do not show an increase in teratogenic effects, spontaneous abortions, or adverse pregnancy outcomes. Based on available human data, and animal reproductive toxicology studies that showed an increase in embryofetal loss, the risk of Coartem exposure during pregnancy does not warrant a ^{(b) (4)}. With the

increase in resistance to antimalarial drugs, pregnant women need to be treated with the most effective drug available. The decision to use Coartem during pregnancy is an individual risk-benefit decision that needs to be made based on the potential benefit of using the drug vs. the potential risk to the developing fetus; by providing available animal and human data in the label, even if limited, women and their health care providers will be able to make a more informed decision.

In order to address some of the limitations of the pregnancy registry, and continue ongoing pregnancy surveillance, the sponsor should consider establishing an international antimalarial pregnancy exposure registry, perhaps in collaboration with other antimalarial drug developers, and international agencies like the WHO.

RECOMMENDATIONS

1. (b) (4)
2. Assign a Pregnancy Category C
3. The sponsor should continue pregnancy exposure surveillance and consider establishing an international pregnancy exposure registry
4. For the final pregnancy registry report, the sponsor should reclassify spontaneous abortion, stillbirth, neonatal deaths, perinatal mortality, and maternal mortality according to standard U.S. definitions, as discussed in this review, and in their final report should report their results according to these definitions
5. The sponsor should do a pK study in pregnant women to determine appropriate dosing that will optimize the chance for effective therapy. This may be important for preventing the development of drug resistance as well.
6. The sponsor should do a lactation study. The sponsor should submit a draft protocol for review within six months of approval.
7. Based on the above review, the MHT recommends the following revisions to the sponsor's proposed Pregnancy and Nursing Mothers sections of the Coartem label (recommended additions are underlined and deletions are struck out):

8.1 Pregnancy

(b) (4)

(b) (4)



Data from a pregnancy registry of approximately 500 pregnant women who were exposed to Coartem, and published data of over 1,000 pregnant patients who were exposed to artemisinin derivatives did not show an increase in teratogenic effects over background rate. (b) (4)

Coartem should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

(b) (4)



Pregnant rats dosed during the period of organogenesis, at or higher than a dose about half the clinical dose (based on body surface area comparisons), showed increases in the number of dead fetuses, early resorptions and post implantation losses. No adverse effects were observed in animals dosed at 0.3 times the clinical dose. Similarly, dosing in pregnant rabbits at about three times the clinical dose (based on body surface area comparisons) resulted in abortions, preimplantation losses, post implantation losses and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at about two times the clinical dose (based on body surface area comparisons). Embryo-fetal loss is a significant reproductive toxicity. Due to a complex metabolic profile in animals and humans, it is not possible to directly compare animal and human exposures to artemether.

8.3 Nursing Mothers

(b) (4) It is not known whether Coartem is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Coartem is administered to a nursing woman. Animal data suggest excretion into breast milk (b) (4)

The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to Coartem through breast milk.

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

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: **November 10, 2008**

From: Carrie Newcomer, Pharm.D.
Kathleen Klemm, Pharm.D.
Division of Drug Marketing, Advertising, and Communications

To: Gregory DiBernardo
Regulatory Project Manager,
Division of Special Pathogen and Transplant Products

Subject: **DDMAC draft labeling comments**
NDA 22-268 Coartem (artemether/lumefantrine) tablets

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the proposed product labeling (PI), proposed patient labeling (PPI), carton, and container labels for Coartem submitted for consult on August 7, 2008, and offers the following comments.

PROPOSED PI

Section 1, Indications and Usage

(
b
)
(
4
)



Section 2.1, Dosage in patients with mild to moderate renal or hepatic impairment

(
b
)
(
4
)



Section 2.2, New and recrudescent infections

(b) (4)



Section 5.1, Prevention of Malaria/Section 5.2, Severe Malaria

- Should these sections be moved into the Indications section and put under a header such as "Limitations of the approved indication?"

Section 5.3, Risk of QTc Prolongation

(
b
)
(
4



Section 6.1, Adverse Reactions – Clinical Studies Experience

(b) (4)



Section 7, Drug Interactions

(b) (4)



Section 7.4, Drug Interactions – Interaction with CYP450 enzymes

(b) (4)



|



Section 8.5, Geriatric Use

(b) (4)



Section 8.6, Use in Specific Populations – Renal Impairment

(b) (4)



Section 12.1, Mechanism of Action

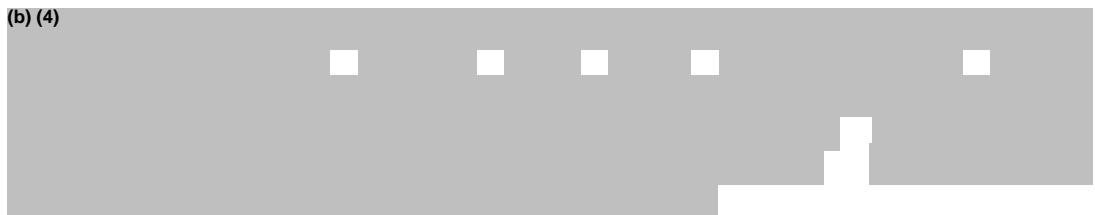
(b) (4)

(b) (4)



Section 12.2, Clinical Pharmacology – Microbiology – Drug Resistance

(b) (4)



Section 12.4, Clinical Pharmacology – Pharmacokinetics – General Comment

(b) (4)



Section 12.4, Clinical Pharmacology – Pharmacokinetics – Biotransformation

(b) (4)



(b) (4)



Section 12.4, Clinical Pharmacology – Pharmacokinetics – Elimination

(b) (4)



PROPOSED CARTON AND CONTAINER LABELS

DDMAC has no comments at this time.

Thank you for the opportunity to comment on this proposed label.
If you have any questions, please contact Katie Klemm at 301.796.3946 or
Kathleen.klemm@fda.hhs.gov

PROPOSED PPI

DDMAC has reviewed the proposed patient labeling (PPI) for Coartem and we offer the following comments. Many of the revisions involve more patient-friendly language and organization. The average consumer reads at an eighth grade level.

Currently, FDA does not have a guidance or standard template for PPIs. We recommend referring to DRISK for their review of this proposed PPI for comments on formatting, order of presentation, consistency, and readability.

If you have any questions or concerns regarding my comments, please contact me.

General Comment

- Please consider bullet format under the headings to highlight certain important information. This serves to increase the readability of the PPI.
- Throughout the PPI, prescriber, doctor, physician, and healthcare provider are used inconsistently. Please consider using one consistently in order to reduce confusion for the patient.
- Throughout the PPI, pills and tablets are used inconsistently. Please consider using one consistently.

Title/Introductory Paragraph

- Please consider deleting “and malaria treatment” from the introductory paragraph. The indication is generally not included in this section of the PPI. Additionally, “malaria treatment” is promotional and broadens the indication for Coartem since the proposed approved use is limited to acute uncomplicated malaria due to infections with

Plasmodium falciparum^{(b) (4)} . Therefore, we recommend deletion.

What is the most important information I should know about Coartem?

- This section typically discusses serious risks associated with the product. Is the statement, “Coartem should be taken with food” the most important information patients should know about Coartem? If so, we recommend adding context to this statement in consumer friendly language to inform patients *why* it is important to take this product with food (because the risk of recrudescence may be greater).
- The statement^{(b) (4)} broadens the indication for Coartem since the proposed approved use is limited to acute uncomplicated malaria due to infections with *Plasmodium falciparum*^{(b) (4)}. If this statement is the most important information patients should know about the product, we recommend revising it to “Take Coartem exactly as prescribed.” This statement seems appropriate to include under the section “**How should I take Coartem?**”

What is Coartem?

- This section currently states,^{(b) (4)} broadens the indication for Coartem since the approved use is limited to acute uncomplicated malaria due to infections with *Plasmodium falciparum*^{(b) (4)}. Therefore, we recommend adding context to this section to present the full indication of Coartem in consumer-friendly language. For example, “Coartem is approved to treat simple cases of malaria caused by the parasite, *Plasmodium falciparum*. Coartem is not approved to prevent malaria or to treat severe cases of malaria.”
- The statement^{(b) (4)} This statement broadens the indication of Coartem (as previously stated, it implies that it is approved for the treatment of all types of malaria). The statement also minimizes the risks of Coartem by associating its side effects with side effects of “all medications.”

Who should not take Coartem?

- This section is generally used to communicate the Contraindications section of the PI to the patient. Please consider including a list of all of the Contraindications to Coartem in consumer-friendly language.
- Please consider bullet format to increase the readability.

What should I tell my doctor before taking Coartem?

- This section is generally used to communicate the Warnings and Precautions information from the PI to the patient; however this section currently lists several Contraindications to Coartem. Please consider relocating the Contraindications to the section “**Who should not take Coartem?**” and revising this section to present the Warnings and Precautions from the PI.
- Please consider bullet format to increase the readability.

- The term “Neuroleptics” is not likely to be understood by consumers (this is listed as a Contraindication in the draft PI and therefore, should be relocated to the section “**Who should not take Coartem?**”)

How should I take Coartem?

- We recommend including the statement, “Take Coartem exactly as prescribed.”
- The statement, “Coartem is a standard 3-day course treatment scheduling consisting of a total of 6 doses” is not likely to be understood by consumers. We recommend revising this statement to be in consumer-friendly language (for example, “Your healthcare provider will prescribe the number of Coartem tablets you will need based on your weight. Unless you are directed otherwise by your healthcare provider, you will take your first dose of Coartem ^{(b) (4)} (s), and then after 8 hours you will take your second dose of Coartem tablet(s). Then you will take your dose of Coartem tablet(s) two times daily (in the morning and evening) for the next 2 days.”)

(b) (4)



Call your healthcare provider right away if:

- Please consider adding this section to communicate to the patient when it is most important to call their healthcare provider (for example, if a patient deteriorates while taking Coartem).

What are the possible side effects of Coartem?

- Please consider bullet format to present the most common side effects of Coartem.
- Please consider deleting the phrase ^{(b) (4)} (emphasis added) This opening phrase frames the rest of this paragraph to be overly reassuring which minimizes the risks of possible side effects.
- The terms “arthralgia” and “myalgia” are not likely to be understood by consumers. We recommend revising these terms to present them in consumer friendly language (for example, “pain or stiffness in joints” and “muscle pain”)
- The draft PI lists “cough” occurring in 23% of children and ^{(b) (4)} Consider adding these two adverse reactions in consumer friendly language to the list of common side effects in the PPI.

What else should I know about Coartem?

- This section discusses that some healthcare providers may prescribe Coartem for self-administration. This discussion is presented in the draft PI under the “Dosage and Administration” section. Please consider relocating this discussion under the heading “**How should I take Coartem?**” in the PPI.
- We recommend revising this section to present it in consumer friendly language.

What is Malaria?

This section states, (b) (4)



How should I store Coartem?

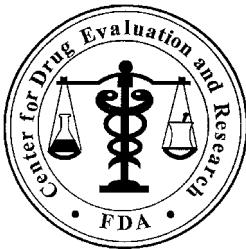
- Please consider adding this section to communicate how to store Coartem properly.
-

Thank you. If you have any questions, please contact Carrie Newcomer at 301.796.1233 or
Carrie.Newcomer@fda.hhs.gov

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/s/

Kathleen Klemm
11/10/2008 03:57:40 PM
DDMAC REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 7, 2008

To: Renata Albrecht, MD
Division of Special Pathogens and Transplant Products

Through: Todd Bridges, RPh., Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Coartem (Artemether and Lumefantrine) Tablets
20 mg/120 mg

Application Type/Number: NDA# 22-268 (IND# 75,287)

Applicant: Novartis Pharmaceuticals Corporation

OSE RCM #: 2008-1280

CONTENTS

EXECUTIVE SUMMARY	1
1 BACKGROUND	1
1.1 Introduction.....	1
1.2 Regulatory History.....	1
1.3 Product Information	1
2 METHODS AND MATERIALS	2
2.1 Label and Labeling Risk Assessment	2
3 RESULTS.....	3
3.1 Label and Labeling Risk Assessment	3
4 DISCUSSION	3
5 CONCLUSIONS and RECOMMENDATIONS.....	3
5.1 Comments to the Division.....	3
5.2 Comments to the Applicant.....	4
A. General Comment (Container labels and Carton Labeling)	4
B. Package Insert Labeling	4
APPENDICES.....	5

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the insert labeling is confusing. The dosing recommendations within the “Dosage and Administration” area of the ‘Highlights of Prescribing Information’ section does not refer to the table which follows it. Additionally, on the container label and carton labeling the established name is less than half the size of the proprietary name and does not have the prominence 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). We have provided recommendations in Section 5.2.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Special Pathogens and Transplant Products to evaluate the container label, carton and insert labeling for the proposed trade name, Coartem.

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis found the proprietary name, Coartem unacceptable in our review dated April 14, 2008 (OSE# 2007-1691) based upon look-alike similarities with Comtan, in accordance with 21 CFR 201.10(c)(5).

In response to our objection, the Applicant submitted a rebuttal that focuses on the low likelihood of confusion that would lead to medication error between Coartem (Artemether and Lumefantrine) 20 mg/120 mg and Comtan (Entocapone) 200 mg. Subsequently, DMEPA reversed the initial decision and found the proposed proprietary name, Coartem, acceptable (OSE# 2008-1039).

1.3 PRODUCT INFORMATION

Coartem (Lumefantrine and Arthemether) is formulated in a fixed-dose combination tablet of Artemether 20 mg and Lumefantrine 120 mg. It is indicated for the treatment of malaria infections and is administered in the following manner:

Adults and children weighing 35 kg and above:

At diagnosis, the patient receives four tablets, then four tablets 8 hours later, and four tablets twice daily (morning and evening) on each of the following two days (total course = 24 tablets).

Infants and children weighing 5 kg to less than 35 kg:

5 kg to less than 15 kg: At diagnosis the patient receives one tablet, then one tablet 8 hours later, and one tablet twice daily on each of the following two days (total course = 6 tablets).

15 kg to less than 25 kg: At diagnosis the patient receives two tablets, then two tablets 8 hours later, and two tablets twice daily on each of the following two days (total course = 12 tablets).

25 kg to less than 35 kg: At diagnosis the patient receives three tablets, then three tablets 8 hours later, and three tablets twice daily on each of the following two days (total course = 18 tablets).

In countries where the product is registered and malaria is endemic, lumefantrine 120 mg and artemether 20 mg is available under the name, Coartem, while in other countries it is known as Riamet.

Coartem will be supplied as a 24 count bottle and as a unit dose carton of 24 tablets (4 x 6-blister cards) for institutional use.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA medication error staff to conduct a label, labeling, and/or packaging risk assessment (see 2.1 Label and Labeling Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labeling and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the U. S. Pharmacopeia-Institute of Safe Medication Practices (USP-ISMP) Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because DMEPA staff analyze reported misuse of drugs, DMEPA staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMEPA uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on June 27, 2008 the following container label, carton and insert labeling for DMEPA to review (see Appendix A, B, C for images):

- Container Label – 24 count bottle, 6 tablet blister card (Appendices A and B)
- Carton labeling - 4 x 6 tablet blister card (Appendix C)
- Package Insert Labeling (no image)

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

The Division of Medication Error Prevention and Analysis notes that the container labels, carton, and insert labeling are vulnerable to confusion and could result in medication errors. We have identified the following areas for improvement.

3.1.1 Container Label and Carton Labeling

The established name is less than half the size of the proprietary name and does not have the prominence 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).

3.1.2 Package Insert Labeling

As currently presented in the ‘Dosage and Administration’ area of the ‘Highlights of Prescribing Information’ Section, the dosing instructions do not refer to the table to reinforce how bodyweight determines the number of tablets needed to achieve the desired dose. The presentation of this information may cause confusion.

4 DISCUSSION

Our Label and Labeling Risk Assessment found that the established name is not prominent which may cause this important information to be overlooked. Additionally, the directions for calculating the dose for this drug product as presented in the table in the ‘Highlights of Prescribing Information’ section are not clear. Specifically, the dosing directions within the ‘Dosage and Administration’ area of the ‘Highlights of Prescribing Information’ section are not linked to the dosing table. There is no statement which refers the reader to the dosing table to explain how the dose is derived. Without this link, the dosing information provided appears fragmented and non-complimentary.

DMEPA also notes the statement, (b) (4) located above the table does not accurately reflect the table content since its relevance appears to be to convey to the user that the proper dose is calculated based upon the weight of the patient. Therefore, this statement does not add value to the information in the table and may confuse the user.

5 CONCLUSIONS AND RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

We have identified areas of needed improvement in the package insert and on the container label and provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Darrell Jenkins, OSE project manager, at 301-796-0558.

5.2 COMMENTS TO THE APPLICANT

A. GENERAL COMMENT (CONTAINER LABELS AND CARTON LABELING)

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).

B. PACKAGE INSERT LABELING

DMEPA notes that the dosing recommendations within the ‘Dosage and Administration’ area of the ‘Highlights of Prescribing Information’ section do not refer to the table which follows it to reinforce how to achieve the desired dose. Without this link, the table does not add value to this section. Additionally, the statement, (b) (4) located above the table does not accurately reflect the table content since the intent of the table is to convey to the user that the proper dose is calculated based upon the weight of the patient.

We therefore, recommend a change in the sentence just prior to the table and a change to the table itself to the following:

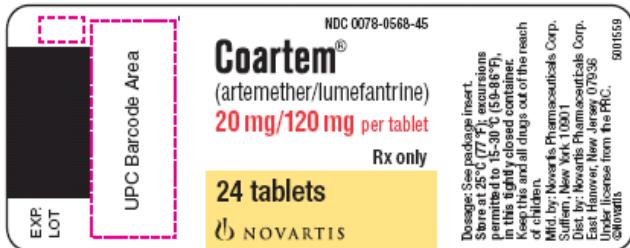
“The number of tablets per dose is determined by body weight using the chart below:”

Table 1.

Patient Weight	Tables Per Dose
5 kg to < 15 kg	1 tablet
15 kg to < 25 kg	2 tablets
25 kg to < 35 kg	3 tablets
35 kg and over	4 tablets

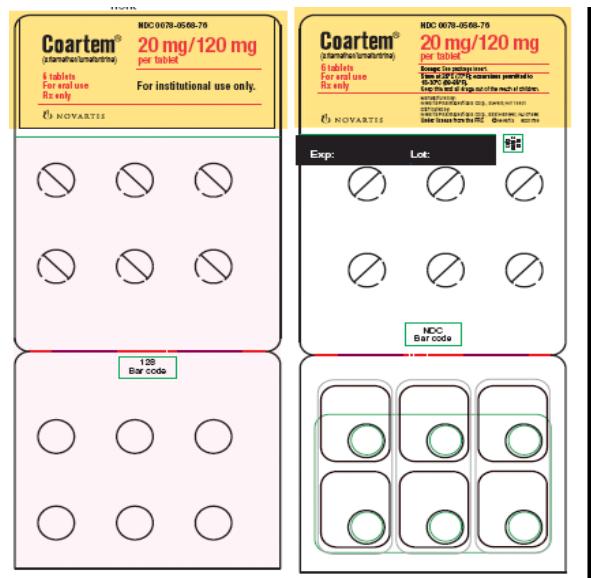
APPENDICES

Appendix A: Container Label

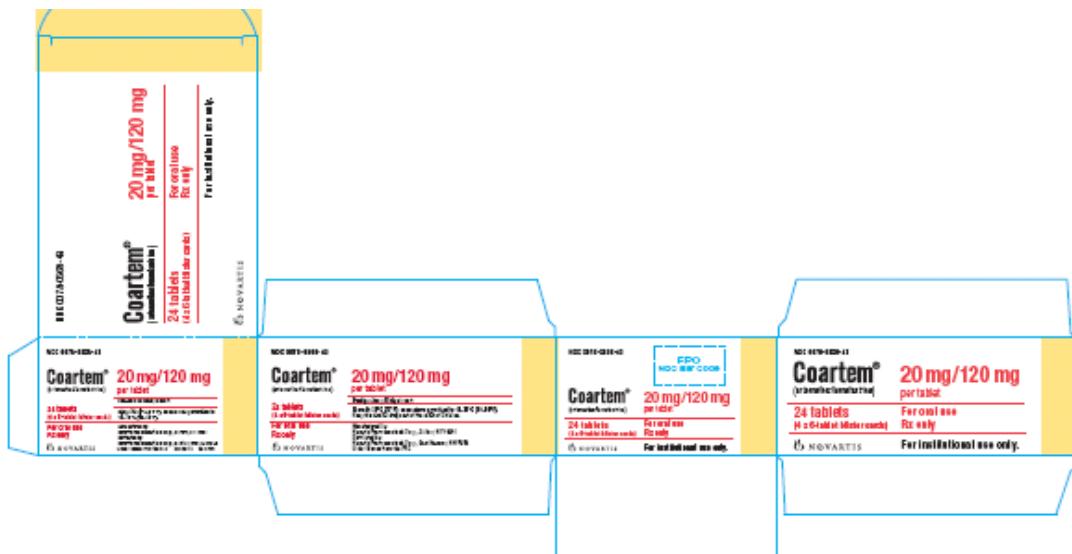


24 count bottle

Appendix B: Blister Label (6 tablet blister card)



Appendix C: Carton Labeling (for 4 x 6 tablet blister card)



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

/s/

Denise Baugh
11/7/2008 04:01:40 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/7/2008 04:04:20 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/7/2008 04:15:47 PM
DRUG SAFETY OFFICE REVIEWER

REQUEST FOR CONSULTATION

TO (*Office/Division*): Division of Neurology Products (DNP)

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

DATE
October 2, 2008

IND NO.
PIND 75,287

NDA NO.
22-268

TYPE OF DOCUMENT

DATE OF DOCUMENT
October 30, 2007
(Nonclinical) and June
27, 2008 (Clinical)

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

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Antimalarial (4050120)

DESIRED COMPLETION DATE
November 10, 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/EPIDEMILOGY 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:

REGULATORY BACKGROUND

Novartis submitted Coartem, NDA 22-268, on a rolling review process, with the last part of the NDA submitted on June 27, 2008, for the indication of treatment of acute, uncomplicated Plasmodium falciparum malaria infection in patients with a bodyweight of 5 kg and above. Coartem was granted a Priority Review and the PDUFA goal date is December 27, 2007 (internal goal date of December 22, 2007). An Advisory Committee meeting is scheduled for December 3, 2008.

Coartem is an NME and an oral fixed-dose combination tablet containing artemether 20 mg and lumefantrine (previously known as benflumetol) 120 mg; both compounds are blood schizonticidal in the life-cycle of Plasmodium species. Artemether has a short half-life and a rapid onset of action and lumefantrine has a slow onset of action and the combination of these two compounds may reduce the emergence of resistance. Coartem

has been marketed outside the U.S. since 1999.

(b) (4)

A 4-dose regimen was initially considered in the drug development plan but was abandoned in favor of the 6-dose due to better efficacy. However, safety data has been submitted for both dosing regimens and is included in the safety analysis for dose-response effects.

NONCLINICAL BACKGROUND FOR CONSULT

In animal models, artemisinin derivatives, such as artemether, have been associated with neurotoxicity, focused on pathways involved in hearing and balance. Such effects appear to occur with high doses of liposoluble compounds administered parenterally; oral administration and water-soluble compounds appear to be far less toxic due to a large first pass effect. Although, neurotoxicity of this type has not been seen in humans, concerns have been expressed regarding the possibility of neurological effects in humans. Lumefantrine appears not to be neurotoxic.

From our review of the Coartem submission, to date, artemether has been shown to cause neuronal necrosis in multiple regions of the brain of beagle dogs following IM administration of 10 mg/kg/day for 8 days. However, brain histopathology was not observed at the highest oral dose of 600 mg/kg/day for 8 days. In addition, no brain histopathologic effects were seen following oral repeat-dose studies of 28 days and longer. Finally, no compound-related clinical neurophysiologic effects were observed at any IM repeat-dose level (up to 80 mg/kg/day) or any oral repeat-dose level (up to 600 mg/kg/day).

Artemether exposure (AUC) is equivalent between 10 mg/kg IM and 600 mg/kg oral. Studies with oral 14C-artemether indicate that the drug undergoes extensive and rapid first pass metabolism to multiple metabolites. Following multiple IM dosing the plasma concentrations of artemether increase, whereas with oral multiple dosing the concentrations of artemether decrease; which suggests that artemether appears to induce its own metabolism.

Due to the pharmacokinetic differences between IM and oral dosing of artemether, it may be that the risk of neurotoxicity is low for humans treated with oral Coartem.

A summary of over 100 nonclinical study reports investigating the safety of artemether, lumefantrine, or the combination has been reviewed by the division.

The Nonclinical Overview Section of the NDA can be found at:

\FDSWA150\NONECTD\N22268\R_001\2007-10-30

In addition, DSPTP's nonclinical summary can be found in Appendix 1.

CLINICAL BACKGROUND FOR CONSULT

Neurotoxicity (i.e., involving hearing and balance) has not been seen to date in humans treated with artemisinin derivatives, even following repeated exposure. However, concerns have been expressed regarding the possibility of neurological effects in humans.

From our review of the Coartem submission, to date, we have not observed any significant neurotoxicity with either the 4-dose or 6-dose regimens in adult or pediatric patients. Postmarketing data on nervous system disorders includes non serious cases of headache or dizziness, and 6 single serious cases (flaccid paralysis of lower limbs; facial paralysis and spasmodic movements of one arm; extrapyramidal syndrome; abnormal behavior, vertigo, dysarthria and abnormal coordination; clonic jerking; mental aberration).

An analysis of ear and auditory adverse events is still ongoing.

The Clinical Overview Section of the NDA (containing the Overview of Safety) can be found at:

\FDSWA150\NONECTD\N22268\N_000\2008-06-27

Pooled safety datasets can be found at: \\Fdswa150\\NONECTD\\N22268\\N_000\\2008-06-27\\crt\\datasets\\Pool

Postmarketing data can be found at: \\Fdswa150\\nonectd\\N22268\\N_000\\2008-09-10

A summary of the clinical safety analysis for nervous system disorders can be found in Appendix 2.

SPECIFIC QUESTIONS TO DNP:

Given the known effects of artemisinin in animals and the potential for neurotoxic effects in humans, it is important that a comprehensive nonclinical and clinical safety evaluation for Coartem is performed. Therefore, we are seeking additional perspective and advice from DNP to complete our analysis of this potential safety issue. Specifically,

1. Upon review, do you consider the applicant's nonclinical and clinical evaluation of neurotoxicity to be adequate?
2. Do you have any concerns or comments about the monitoring for neurologic events, or lack of monitoring, in the clinical trials? Do you have any suggestions for testing that should be incorporated into future trials?
3. Do you agree with DSPTP's preliminary nonclinical and clinical analyses? Do you have any additional comments to add?
4. Do you have any comments regarding labeling of this product if it were approved for the treatment of acute, uncomplicated malaria in adults and children as a 3 day regimen?
5. DSPTP is planning to request two nonclinical studies as post-marketing commitments (PMCs). Are there other nonclinical or clinical studies you would recommend, either prior to approval or as PMCs?

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

Thank you for your assistance.

SIGNATURE OF REQUESTOR Gregory DiBernardo	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

APPENDIX 1

DSPTP's Nonclinical Neurotoxicity Safety Summary

NEUROLOGIC TOXICITY FINDINGS:

The applicant submitted neurotoxicity studies in beagle dogs that indicated compound-related histopathology in several regions of the brain following intramuscular (*im*) administration of artemether for 7 or 8 consecutive days. The NOAEL for brain histopathology by *im* administration was 10 mg/kg. Brain histopathology was not observed following repeat oral administration of artemether doses of 300 and 600 mg/kg/day. Lumefantrine appears to not be neurotoxic.

- Lesions observed after *im* dosing of artemether included chromatolysis, microgliosis, neuronal necrosis, axonal swelling, neurofilament clumping, eosinophilic cytoplasmic granulation, and spheroids.
- Areas prominently affected included pontine nuclei, cerebellar nuclei, nucleus vestibularis, nucleus hypoglossus, and nucleus cuneatus.
- Additionally, lesions were noted in the nucleus cochlearis, formatio reticularis, colliculus caudalis, nucleus nervi trigemini, nucleus olivaris, nucleus ambiguus, and cerebral cortex.
- Regions of brain associated with hearing and not exhibiting histopathology included the ganglion spirale, vestibule-cochlear nerves, and conti's organ.

PHARMACOKINETICS:

- Metabolism disposition data with ¹⁴C-labelled artemether indicated substantial absorption by dogs of orally administered artemether. Approximately 60 percent of the radioactive dose was excreted in urine suggesting that at least 60 percent of the oral dose was absorbed in the G.I. tract.
- HPLC/ radioactivity analysis of plasma samples indicated that ¹⁴C-artemether was rapidly metabolized following oral dosing to multiple metabolites as a result of first pass metabolism, accounting for its low plasma AUC values.
- Plasma artemether Cmax and AUC values at the 10 mg/kg *im* dose (NOEL for brain histopathology) were equivalent to the values obtained following the 600 mg/kg oral artemether dose on Day 1.
- Artemether and dihydroartemisinin (initial metabolite) both appear to be minor components in plasma at 2 hours following oral dosing. Two other plasma metabolites were more prominent then, but metabolite peaks were not structurally characterized.
- Artemether was detected/quantitated in the CSF following *im* dosing, but at a fraction of the corresponding plasma artemether concentrations. Dihydroartemisinin was not detected in the CSF. Artemether was not detected in the CSF following the 600 mg/kg oral dose.

DSPTP's INITIAL REQUEST TO APPLICANT:

In order to better understand the relative exposures of dogs and humans so we can better evaluate the potential for adverse neurologic effects in humans, DSPTP recently requested the following from the NDA 22-268 applicant:

- 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.

ADDITIONAL REQUESTS:

DSPTP is planning to request the following two nonclinical studies as post-marketing commitments:

Post-Dose Neurotox Evaluation following repeat *im* dosing

Beagle dogs (can be males or females only) receiving repeat *im* dosing for 7 or 8 days at dose levels of 0, 40, and 80 mg/kg/day. All dogs to be held for a two or four week post-dosing period. Clinical neurologic function tests (as described in studies submitted by the applicant in the NDA) following the final dose and at one-week post dosing intervals. Information from this study is needed in order to determine if neurologic deterioration occurs following the final dose administration that results in observations of impaired neurologic function. Impairment of neurologic function was not observed in the studies submitted by the applicant, however, all animals were sacrificed for histopathology 24 hours following the final dose.

Pathology and histopathology are optional in the proposed study; if included they can be limited to brain histopath in the areas previously shown to have histopathologic effects.

Metabolism/Disposition study in dogs with radiolabelled artemether

Beagle dogs (can be male or female) receive single *im* dose and single oral dose of radiolabelled artemether (40 mg/kg *im* and 300 mg/kg oral). Determination of plasma pharmacokinetics for total radioactivity, plasma profile for radioactivity (HPLC/radioactivity flow analysis, plasma PK for artemether, and plasma PK for two or three of the major metabolites in plasma (requires previous structural identification of the metabolites in plasma)). The urinary and fecal excretion of radioactivity also needs to be assessed in this study. This study will provide some understanding regarding the effect route of administration has upon plasma concentrations for artemether and its metabolites and the possible impact upon the difference in observed neurotoxicity (histopathologic effects) that appears to be dependent upon the route of administration.

ADDITIONAL BACKGROUND:

Neurotoxicity Studies with Beagle Dogs

COA566: 8-Day Exploratory Neurotoxicity Study in Dogs (Study no. 0410073):

40 mg/kg/day im doses for eight consecutive days:

Compound-related histopathology (chromatolysis, eosinophilic cytoplasmic granulation, and spheroids) in eleven different brain locations (nuclei) primarily in the brain stem.

Clinical neurophysiologic effects were not observed.

CGP 56696: Pilot Intramuscular Neurotoxicity Study in Dogs with Pharmacokinetics (Test no. 96-6141):

20 mg/kg im doses for 5 or 30 consecutive days:

No compound-related effects after five days of dosing.

Neurologic histopathologic effects following 30 days of dosing; brain neuronal chromatolysis, microgliosis and necrosis (severity classified as minimal to mild).

Clinical neurophysiologic effects were not observed.

CGP 56696: Oral and Intramuscular Neurotoxicity Study in Dogs with Pharmacokinetics (Test no. 97-0024):

Artemether administered im - 0, 20, 40, and 80 mg/kg/day or Orally - 0, 50, 150, and 600 mg/kg/day for eight consecutive days:

Neurologic histopathologic effects observed in males and females at each im-dose level. The frequency and severity of these lesions exhibited a dose response relationship.

Brain regions that were analyzed included the cerebellar nuclei, pontine nuclei, vestibular nuclei, and the paralemniscal/raphe.

Histopathologic effects were not observed at any oral dose level.

Clinical neurophysiologic effects were not observed in males and females from any of the *im* and oral dose levels.

ARM 566: Intramuscular Neurotoxicity Study in Dogs (Study no. 510001):

Single 10 and 40 mg/kg im doses of Artemether for 3 or 8 consecutive days to male beagle dogs:

Compound-related neurologic histopathologic effects were only observed in dogs dosed for 8 days at 40 mg/kg/day. **NOEL** 10 mg/kg for 8 consecutive days.

No compound-related effects on brainstem auditory evoked potentials (BAEP).

Clinical neurophysiologic effects were not observed.

*CoA 566 and ARM 566: Oral Neurotoxicity Study in Dogs (Study No. 0510009):
Single daily oral doses of artemether at 600/300 mg/kg/day & artemether plus lumefantrine for 3 or 8 consecutive days.*

600 mg/kg artemether **oral dose** was reduced to 300 mg/kg following the first dose due to excessive toxicity.

Clinical neurophysiologic effects were not observed following the terminal dose.

No compound-related effects on **BAEP**.

Compound-related neurologic histopathologic effects were not observed following the oral dosing regimens.

Comprehensive Brain Histopathology

Regions of the brain examined by histopathology in the comprehensive studies with dogs following *im* administrations of artemether and oral administrations of artemether and lumefantrine.

Ganglion spirale (left & right)	Corpus geniculatum mediale	Nucleus ruber
Vestibule-Cochlear nerves	Cortex temporalis	Nucleus ambiguus
Corti's Organ	Hypothalamic nuclei	Nucleus hypoglossus
Nucleus cochlearis dorsalis	Thalamic nuclei	Nucleus cuneatus
Nucleus cochlearis ventralis	Pontine nuclei	Nucleus gracilis
Formatio reticularis	Pons (central gray)	Nucleus vagus
Nucleus olivaris superior	Nucleus nervi trigemini	Nucleus olivaris
Corpus trapezoideum	Cerebellar nuclei	Cerebellum
Leminiscus lateralis	Nucleus vestibularis lateralis	Remaining white matter
Colliculus caudalis	Nucleus vestibularis medialis	Remaining gray matter

Clinical Neurologic Evaluations

Acoustic response	Hopping response	Patellar reflex
Activity	Landing response	Pupil reflex
Bicipital reflex	Menace response	Placing reactions (visual and tactile)
Extensor strength (muscular)	Muscle tone	Posture
Flexor reflex	Muscle wasting	Proprioceptive placing
Gait	Nystagmus	Wheel barrowing
Muscle coordination	Sensor motor functions	Neck reflex

Artemether Toxicokinetics in Beagle Dog Neurotoxicity Studies

TK after 7 Days *in Dose Administration*

Artemether Dose Levels	Artemether		Dihydroartemisinin	
	Cmax ($\mu\text{g}/\text{ml}$)	AUC ($\mu\text{g} \cdot \text{hr}/\text{ml}$)	Cmax ($\mu\text{g}/\text{ml}$)	AUC ($\mu\text{g} \cdot \text{hr}/\text{ml}$)
10 mg/kg	0.21	1.8	0.03	0.26
20 mg/kg	0.29	5.4	0.02	0.31
40 mg/kg*	0.55 - 0.83	7.5 - 12.8	0.02 - 0.03	0.34 - 0.47
80 mg/kg	1.18	20.8	0.03	0.49

* Range in values from three separate studies.

Artemether Cerebrospinal Fluid Concentrations

2 hours following terminal dose on Day 8

Dose Level	CSF ($\mu\text{g}/\text{ml}$)	CSF/Plasma ratio
20 mg/kg	0.025	0.086
40 mg/kg	0.060	0.077
80 mg/kg	0.071	0.060

[Dihydroartemisinin was not detected in the CSF.]

Artemether Cmax and AUC values following oral administration

	Artemether		Dihydroartemisinin	
	Cmax ($\mu\text{g}/\text{ml}$)	AUC ($\mu\text{g} \cdot \text{hr}/\text{ml}$)	Cmax ($\mu\text{g}/\text{ml}$)	AUC ($\mu\text{g} \cdot \text{hr}/\text{ml}$)
600 mg/kg Day 1	0.21	1.73	0.79	6.6
600 mg/kg Day 7	0.03	0.25	---	---
300 mg/kg Day 3	0.13	0.60	0.61	1.39
300 mg/kg Day 7	0.05	0.07	0.14	0.19

^{14}C -Labelled Artemether Absorption, Disposition & Plasma Profile in Beagle Dogs

Dose Formulations:

10 mg/kg iv = 1.43 mg/kg ^{14}C -artemether plus 8.57 mg/kg lumefantrine

20 mg/kg oral = 2.86 mg/kg ^{14}C -artemether plus 17.14 mg/kg lumefantrine

200 mg/kg oral = 28.6 mg/kg ^{14}C -artemether plus 171.4 mg/kg lumefantrine

Approximately 60 percent of radioactivity is derived from ^{14}C -artemether excreted in urine following 20 or 200 mg/kg oral dose of co-artemether, suggesting at least 60 percent intestinal absorption of orally administered ^{14}C -artemether.

Plasma profile of ^{14}C -labelled products indicated no quantifiable levels of ^{14}C -artemether at 2 hours following orally administered 20 and 200 mg/kg ^{14}C -artemether containing co-artemether doses. Among multiple ^{14}C -labelled metabolites detected in plasma, dihydroartemisinin appears to be a minor metabolite compared to other radiolabelled metabolite peaks (not identified).

10 mg/kg *iv* dose of co-artemether: approximately 53 percent of the radioactivity derived from ^{14}C -artemether excreted in urine and 33 percent excreted in feces (possible biliary elimination of radioactive metabolites).

Plasma ^{14}C -artemether levels declined rapidly following the *iv* administration of the 10 mg/kg co-artemether dose. Plasma AUC values for total plasma ^{14}C , ^{14}C -artemether, and ^{14}C -dihydroartemisinin:

Total Plasma ^{14}C	138 $\mu\text{mol} \cdot \text{hr/L}$
^{14}C -artemether	0.81 $\mu\text{mol} \cdot \text{hr/L}$
^{14}C -dihydroartemisinin	0.30 $\mu\text{mol} \cdot \text{hr/L}$

^{14}C -Labelled Artemether Metabolism by Human and Dog Liver Homogenates

Liver fractions (postmitochondrial) from human and dog readily metabolize artemether. [^{14}C -artemether levels *in vitro* diminish substantially between 15 min and 120 min of incubation.]

Multiple radioactive metabolite peaks present in the 15 and 120 min incubations.

Metabolite profiles from dog and human incubations are similar, metabolite ratios appear to differ.

Approximately six defined (baseline resolved) metabolite peaks from incubations with dog liver homogenates and eight defined peaks from incubations with human liver homogenates. [Metabolites were not structurally characterized in this study.]

APPENDIX 2

DSPTP's Clinical safety analysis – Nervous system disorders

BACKGROUND

In animal models, artemisinin derivatives, such as artemether, have been associated with neurotoxicity, focused on pathways involved in hearing and balance. Such effects appear to occur with high doses of liposoluble compounds administered parenterally; oral administration and water-soluble compounds appear to be far less toxic due to a large first pass effect. Neurotoxicity of this type has not been seen in humans (Price, 2000; Ribiero and Olliari 1998), even following repeated exposure to artemisinin derivatives (Kissinger, et al 2000) and no evidence of such neuropathology was observed in a series of autopsies carried out on patients who died due to severe malaria despite treatment with high-dose intramuscular artemether (Hien et al 2003).

However, concerns have been expressed regarding the possibility of neurological effects in humans (Johann-Liang and Albrecht 2003). There have been case reports of neurological problems (including ataxia, nystagmus, tremor and slurred speech), occurring after administration of herbal artemisinin (Panossian, Garga and Pelletier 2005) or artesunate monotherapy (Miller and Panosian 1997, Franco-Paredes, et al 2005), in one case following five 10-day courses of the drug (Franco Paredes, et al 2005), but in each case the attribution of neurotoxicity to artemisinin treatment was questionable (White, Ashley and Nosten 2006; Davis, Edwards and McCarthy 1997; Newton, Day and White 2005). A review of artemisinin-related neurotoxicity can be found in Toovey 2006.

Note: Links to the complete published papers referenced on this page can be found in the Clinical Overview section starting on page 198: \\FDSWA150\NONECTD\N22268\N_000\2008-06-27

In the FDA's review of this submission, AEs related to the nervous system were examined in detail given previous known toxicities of the artemisinin derivatives. Adult (>16 years of age) and pediatric subjects (≤ 16 years of age) were divided into 2 populations for safety analyses.

Two analyses are pending: a review of ear and auditory AEs, and post marketing data on nervous system and auditory AEs reported with co-artemether exposures.

RESULTS TO DATE

In the Applicant's submission, safety data was presented as two pooled analyses: one for adults and adolescents (patients who were >12 years of age), and the other for children and infants (patients ≤ 12 years of age). Given the literature reports of neurologic AEs with co-artemether exposure, and the ongoing neurocognitive development which occurs in adolescence, the FDA chose to include adolescents with pediatrics in the pooled safety analysis. Therefore the FDA

analysis used the following populations:

- Adults (>16 and ≤65 years of age)
- Pediatrics and adolescents (≤16 years of age)

For this reason, the tables which follow differ slightly from the Applicant's tables found in the Clinical Overview section.

Adult pooled safety population

Table 1. Adverse events affecting the SOC “Nervous system disorders”, FDA adult pooled safety population

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose	Coartem 6 dose (tablet)	Mefloquine Artesunate (MAS)
Nervous system disorders	Ataxia	10 (1.28%)	5 (0.78%)	14 (5.00%)
	Clonus	5 (0.64%)	20 (3.10%)	0 (0%)
	Coma	0 (0%)	1 (0.16%)	0 (0%)
	Convulsion	1 (0.13%)	0 (0%)	0 (0%)
	Coordination abnormal	0 (0%)	0 (0%)	1 (0.36%)
	Dizziness	424 (54.22%)	354 (54.88%)	234 (83.57%)
	Dysgeusia	1 (0.13%)	0 (0%)	0 (0%)
	Fine motor delay	0 (0%)	3 (0.47%)	2 (0.71%)
	Headache	591 (75.58%)	476 (73.80%)	255 (91.07%)
	Hypersomnia	1 (0.13%)	0 (0%)	0 (0%)
	Hypoesthesia	3 (0.38%)	4 (0.62%)	7 (2.50%)
	Lethargy	1 (0.13%)	0 (0%)	0 (0%)
	Mental impairment	0 (0%)	1 (0.16%)	0 (0%)
	Nystagmus	8 (1.02%)	5 (0.78%)	16 (5.71%)
	Paraesthesia	32 (4.09%)	0 (0%)	27 (9.64%)
	Somnolence	1 (0.13%)	3 (0.47%)	0 (0%)
	Syncope vasovagal	1 (0.13%)	0 (0%)	0 (0%)
	Tremor	22 (2.81%)	17 (2.64%)	14 (5.00%)
Subjects		782 (100.00%)	645 (100.00%)	280 (100.00%)

There was no apparent dose-response relationship with respect to nervous system AEs, as the rates were comparable between the 4- and 6-dose regimens. The most frequently reported AE in all treatment groups was headache followed by dizziness. These were likely symptoms of malaria, since the onset of most of these AEs was at baseline or before starting study medication.

The only AE which stood out in the 6-dose regimen was clonus (3.1% compared to co-artemether 4 dose 0.6% and MAS 0%). AEs representing balance (PTs ataxia, coordination abnormal, dizziness, nystagmus and tremor) were generally higher in the 4-dose regimen, and may have been a result of differences in reporting methods between studies. While comparisons between groups must be performed with caution, nervous system AEs in the MAS group were reported more frequently than the either co-artemether groups, including the balance AEs mentioned previously.

Table 2 shows the life-threatening and severe AEs in the nervous system disorders SOC. Note both 4- and 6-dose are represented in this table.

Table 2: Severe and life-threatening AEs in the SOC “Nervous system disorders”, FDA’s Adult pooled safety population

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem		MAS
		Life-threatening	Severe	Severe
Nervous system disorders	Coma	1 (0.07%)	0 (0%)	0 (0%)
	Headache	0 (0%)	6 (0.42%)	0 (0%)
	Somnolence	0 (0%)	1 (0.07%)	0 (0%)
	Syncope vasovagal	0 (0%)	1 (0.07%)	0 (0%)

Narratives for the severe and life-threatening AEs in the SOC Nervous system disorders follow:

1. Somnolence

Subject 1 was a 37 year old Caucasian female enrolled in A2401. On study day 2, dizziness, hyperglycaemia, influenza-like illness, myalgia, vaginal haemorrhage and vomiting were reported, all of mild severity. On study day 3, the subject received her last dose of study drug and her blood smear was negative for parasites. Somnolence was also reported on study day 3, the same day that existing vomiting was coded as severe. No action was taken for somnolence, and the AE resolved on study day 4. The subject received domperidone (1 dose) and paracetamol for vomiting and fever/headache respectively on study day 1. It is noted that domperidone overdosage/toxicity includes CNS symptoms of drowsiness, disorientation and extrapyramidal reactions, and that the subject had mild renal impairment at baseline (creatinine 90 umol/L). However, onset of somnolence was on study day 3 and the subject only received 1 dose of domperidone. The investigator felt the severe AE was suspected to be related to study drug.

Reviewer’s comment: The temporal onset and resolution of the severe AE somnolence suggest it could have been related to study drug. There are inadequate details to attribute this AE to domperidone.

2. Syncope vasovagal

Subject 11 was a 33 year old Caucasian male enrolled in A014 who received the co-artemether 4-dose regimen. Prior to the start of the study, he reported the severe AE headache as well as chills, nausea, sleep disorder, and hyperhidrosis. His baseline parasite count was 197 200, rapidly dropped to 45 on day 2, but did not drop to 0 until day 8. On study day 2, the severe AEs syncope vasovagal and fatigue were recorded, both of 1 day’s duration. His blood pressure was 85/50 with a pulse of 76 on this day, both decreased from a baseline blood pressure of 120/80 and pulse 80. All AEs resolved by study day 4. On study day 14, severe asthenia, as well as moderate headache and insomnia were recorded. None of his AEs were felt to be related to study drug. No additional information was available about the subject’s past medical history or

concomitant medications.

Reviewer's comment: The severe headache was likely a symptom of malaria and resolved as his parasite count dropped. There are no details regarding the syncope, such as cardiac history or situation before the event, although the drop in both blood pressure and pulse suggest this was vasovagal in nature.

3. Headache

The 6 subjects with severe headache were reviewed and are presented in Table 3. All were assessed to be not related to study drug.

Table 3. Headaches of severe intensity, FDA adult pooled population

Subject/Study /coartem dose	Subject demographics	Study day headache onset recorded	Study day headache ended	Related to study drug	Comments
11/A014/4 dose	33 yo Caucasian male	-4	5	Unlikely	Also experienced severe AE "vasovagal syncope"
35/A025/4 dose	30 yo female	1	3	Unlikely	Anorexia, arthralgia, asthenia, chills, dizziness, fatigue, myalgia, nausea, vomiting all resolved on study day 3
85/A025/6 dose	19 yo female	1	3	Unlikely	Abdominal pain, anorexia, arthralgia, asthenia, chills, clonus, diarrhea, dizziness, fatigue, myalgia, nausea, palpitations, pruritus, rash, sleep disorder, tremor and vomiting all started on study day 1 and resolved on day 3
103/A025/4 dose	35 yo female	1	8	Unlikely	Present at baseline
9/A2401/6 dose	32 yo Caucasian male	3	3	Unlikely	Last dose of study drug on day 2, onset of severe headache and hyperhidrosis, both 1 day's duration on day 3; no action taken, no information on medications
3/A2401/6 dose	32 yo male	2	4	Unlikely	No AEs reported at baseline (day 1), chills, headache on day 2, malaise, pyrexia and vomiting on day 3. Subject received ibuprofen and paracetamol for headache

The 6 subjects (3 male, 3 female) were equally divided with respect to receipt of 4 or 6-dose co-artemether. Three of the subjects were enrolled in Study A025. Four of the subjects had onset of headache either before or on the same day as receipt of study drug, which makes it less likely to be related to study drug. Similarly, most headaches resolved shortly after completing the course of co-artemether, with only 1 case of headache lasting out to study day 8 (Subject 103).

There were 2 subjects with onset of severe headache after initiating co-artemether on study day 1. Both were not felt to be related to the study drug by the reviewing MO. Subject 9 was a 32 year old male enrolled in A2401 who received the 6-dose co-artemether regimen. He had no AEs recorded other than both severe headache and severe hyperhidrosis on day 3 which resolved in 1

day with no therapy or action. These occurred off study drug. His parasite count dropped to 0 on study day 3 from a baseline of 3980. Subject 3 was also a 32 year old male enrolled in A2401 who also had no AEs at baseline, but had typical malaria symptoms reported on day 2 and 3 including chills, malaise, pyrexia and vomiting in addition to the severe AE headache. His parasite count at baseline was 108 and dropped to 0 by day 2. The headache resolved with medications on day 4 while all other AEs resolved on day 3. While it is possible that the headache was related to co-artemether, the clustering of other typical malaria symptoms at the same time the headache was reported makes it less likely.

All SAEs within the Nervous system disorders SOC were reported in the 6-dose group. There was 1 case each of coma, headache and mental impairment. The narratives for these SAEs are presented below. None of these SAEs were felt to be related to study drug.

1. Subject 7

Subject 7 was a 55 year old Caucasian female enrolled in A2401 with a history of bronchopneumonia, appendicitis and peritonitis with the following SAEs requiring hospitalization: blood bilirubin increased, transaminases increased, mental impairment, disease progression and vomiting. At baseline, her bilirubin was elevated at 33 umol/L (reference range 7-25 umol/L), as well as both SGPT and SGOT at 105 U/L (reference range 9-42 U/L). On study day 2, SGOT and SGPT increased to 287 and 162 U/L respectively, with bilirubin 90 µmol/L. The subject received 2 of the 6 doses at the time mental impairment and increased liver enzymes were reported. Study medication was held on April 29 and the subject received IV quinine (possibly for the SAE “disease progression”, i.e. cerebral malaria and the presence of *P. falciparum* asexual forms on day 2 sample). Mental impairment resolved and co-artemether was restarted on April 30. The subject therefore received the 6 doses of co-artemether over 5 days (April 27 to May 2). When co-artemether was reintroduced, liver tests remained within normal ranges and blood bilirubin increased, transaminases increased, and disease progression SAEs were all recorded as resolved on May 3. The increased bilirubin and transaminases, mental impairment and vomiting were all coded as “suspected” relationship to study drug by the investigator. The subject also received paracetamol for fever but information regarding the number of doses she received was not recorded.

Reviewer's comment: Mental impairment, disease progression and vomiting were likely due to malaria. While the baseline increased bilirubin and transaminases were likely due to malaria, it is not possible to determine if the worsening of these lab parameters on day 2 were a result of study drug, ongoing malaria or paracetamol.

2. Subject 2

Subject 2 was a 62 year old Caucasian female enrolled in A2401. She received her last dose of co-artemether on Dec 1, with onset of the following SAEs 19 days later on Dec 20: chills, pyrexia, headache, and *plasmodium falciparum* infection. She was hospitalized and received Malarone on Dec 21 and *P. falciparum* asexual forms were seen on a blood smear on Dec 22. She received Malarone for 3 days and made a complete recovery. These SAEs were resolved by Dec 24 and were malaria infection symptoms.

3. Subject 259

Subject 259 was a 17 year old male in Study A026 with the SAE coma. He presented at baseline with anorexia, dizziness, fever, chills, headache, nausea, vomiting, arthralgia, myalgia, asthenia, and sleep disorder. All of these AEs resolved by study day 8. Coma was recorded on study day 14. His baseline *P. falciparum* asexual form count was 10 826 and was cleared in 3 days although gametocytes did not clear until day 15. Two days prior to the onset of coma, the subject had experienced fever, chills and feeling unwell (according to subject's sister). He then "became unconscious with fever and vomiting". His temperature on day 15 was 40.5°C. He received phenobarbital, quinine, paracetamol and glucose, and later received chloramphenicol for possible meningitis and diazepam for convulsions. A lumbar puncture was attempted but was not successful. No parasites were found in his blood smear. The subject received ampicillin and metronidazole for aspiration pneumonia for the duration of the SAE. The case report form coded the SAE as "febrile coma, reason unknown". The subject made a complete recovery on day 24. Information regarding follow up was not available.

Reviewer's comment: The etiology of the coma is unclear. Although cerebral malaria would be high on the differential, his parasite count (asexual forms) was negative. There are no CSF results or other laboratory tests which could provide this information. The ampicillin and metronidazole for aspiration pneumonia could have been concurrently treating a cerebral infection. It is unlikely that co-artemether was the cause of this SAE due to the late onset and multiple other explanations which cannot be ruled out.

Pediatric pooled safety population

Table 4. Adverse events affecting the SOC “Nervous system disorders”, FDA pediatric safety population

MedDRA system organ class (V 10.1)		Coartem 4 dose	Coartem 6 dose (crushed tablet)	Coartem 6 dose (dispersible tablet)	Coartem 6 dose (tablet)	Mefloquine Artesunate	SP
Nervous system disorders	Aphasia	1 (0.15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Ataxia	3 (0.46%)	0 (0%)	0 (0%)	1 (0.23%)	5 (3.33%)	0 (0%)
	Clonus	7 (1.06%)	0 (0%)	0 (0%)	11 (2.53%)	1 (0.67%)	0 (0%)
	Convulsion	6 (0.91%)	2 (0.44%)	1 (0.22%)	1 (0.23%)	0 (0%)	1 (0.70%)
	Coordination abnormal	2 (0.30%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Dizziness	153 (23.22%)	1 (0.22%)	0 (0%)	66 (15.21%)	104 (69.33%)	6 (4.20%)
	Dyskinesia	0 (0%)	0 (0%)	1 (0.22%)	0 (0%)	2 (1.33%)	0 (0%)
	Epilepsy	0 (0%)	0 (0%)	1 (0.22%)	0 (0%)	0 (0%)	0 (0%)
	Facial palsy	1 (0.15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Febrile convulsion	1 (0.15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.40%)
	Fine motor delay	8 (1.21%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Headache	369 (55.99%)	33 (7.30%)	34 (7.61%)	114 (26.27%)	137 (91.33%)	56 (39.16%)
	Hyperreflexia	2 (0.30%)	0 (0%)	0 (0%)	6 (1.38%)	0 (0%)	0 (0%)
	Hypersomnia	1 (0.15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Hypokinesia	44 (6.68%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Hypotonia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.70%)
	Lethargy	34 (5.16%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.70%)
	Myoclonus	0 (0%)	0 (0%)	0 (0%)	3 (0.69%)	0 (0%)	0 (0%)
	Nystagmus	4 (0.61%)	0 (0%)	0 (0%)	1 (0.23%)	4 (2.67%)	0 (0%)
	Paraesthesia	4 (0.61%)	0 (0%)	0 (0%)	0 (0%)	4 (2.67%)	0 (0%)
	Somnolence	2 (0.30%)	1 (0.22%)	2 (0.45%)	1 (0.23%)	0 (0%)	1 (0.70%)
	Speech disorder	33 (5.01%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.70%)
	Tremor	3 (0.46%)	1 (0.22%)	0 (0%)	1 (0.23%)	1 (0.67%)	0 (0%)
Subjects		659 (100.00%)	452 (100.00%)	447 (100.00%)	434 (100.00%)	150 (100.00%)	143 (100.00%)

Nervous system AE rates for nearly all PTs were lower with the pediatric population compared to adults, and may be due to the fact that infants and small children cannot report symptoms. Most AEs were reported on study days 1-3. However, the most frequently reported nervous system AEs for all treatment groups were headache and dizziness, which were the same PTs reported with the adult population. Although between group comparisons should be interpreted with caution, headache was most frequently reported with MAS (91.3%) followed by co-artemether 4-dose (56%) and 6-dose (26.3%). The frequency of headache was similar between adults and pediatrics for the MAS groups (91.1% and 91.3% respectively), but the rate of headache was significantly higher in adults compared to pediatrics for the 6-dose tablet co-artemether group (73.8% vs. 26.3%).

AEs were generally higher for the 4-dose compared to 6-dose co-artemether regimens, the exceptions being clonus (6-dose 2.5% vs. 4-dose 1.1%), hyperreflexia (1.4% vs. 0.3%) and myoclonus (0.7% vs. 0%). This similar pattern has been noted with all AEs and was attributed to differences in collecting AEs and study design.

AEs representing balance (PTs ataxia, coordination abnormal, dizziness, nystagmus and tremor) were higher with the 4-dose than 6-dose regimen. They were also higher with the MAS group than either co-artemether groups.

Severe and life-threatening AEs for co-artemether (4 and 6 doses are combined), MAS and SP are shown in Table 6.

Table 5. Severe and life-threatening AEs in the SOC “Nervous system disorders”, FDA pediatric pooled safety population

		Coartem		MAS	SP	
MedDRA system organ class (V 10.1)	Convulsion	Life-threatening	Severe	Severe	Life-threatening	Severe
		0 (0%)	1 (0.05%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders	Headache	0 (0%)	3 (0.15%)	0 (0%)	0 (0%)	0 (0%)

There were only 4 severe and life-threatening AEs in the pediatric population, 3 were headaches and 1 was convulsion. Narratives for the severe and life-threatening AEs in the SOC Nervous system disorders follow. In all the cases, none of the severe AEs were related to study drug.

Convulsion

Subject 46 was a 5 year old black male enrolled in Study B2303 who received Coartem 6-dose as a dispersible tablet. His last dose was Sept 7 and convulsion (severe intensity as well as SAE) was reported on study day 29 (Oct 3) along with mild pyrexia. His parasite count was zero at presentation, he was diagnosed with meningitis and treated with benzylpenicillin.

Headaches:

- Subject 90 was a 12 year old female enrolled in A003 who received co-artemether 4-dose. Severe headache in addition to moderate fatigue, dizziness, nausea, vomiting and chills were noted on study day 1. The headache resolved on day 4, and her parasite count was 0 by day 2. There is no information on concomitant medications.

Reviewer's comment: This subject's headache was likely due to malaria.

- Subject 140 was a 12 year old female enrolled in A003 who received co-artemether 4-dose. Severe headache in addition to moderate fatigue, dizziness, and mild anorexia and chills were present on study day 1 and all resolved by day 2-4 (headache resolved on day 3).

Reviewer's comment: This subject's headache was likely due to malaria.

- Subject 74 was a 6 year old female enrolled in B2303 who received co-artemether 6-dose. She developed severe headache and pyrexia on study day 35 and was diagnosed with *Plasmodium falciparum* infection.

Reviewer's comment: This subject's headache was due to malaria recrudescence.

All SAEs within the Nervous system disorders SOC were reported in the 6-dose group. There were 3 cases of convulsion, 1 case each with the crushed tablet, dispersible tablet and tablet forms. Brief narratives for these SAEs are presented below. In none of the cases was the study drug suspected to be the cause - two of the convulsions were related to cerebral malaria, and the remaining case was due to meningitis.

1. Subject 145 was an 8 month old black female enrolled in A2403. She received her last dose of Coartem on Oct 31 and was clear of parasites. On Nov 24 (study day 28), she presented with convulsion, ear pain and rash. Her parasite count was 19,775. The SAEs plasmodium falciparum infection and convulsion were noted and she was treated with amodiaquine and recovered.
2. Subject 22 was a 2 year old black male enrolled in study B2303 who received Coartem 6-dose as a crushed tablet. His last dose was Jan 13. On study day 42 (Feb 20), he had a convulsion and was diagnosed with malaria. His parasite count was 67,102. Both the convulsion and *P. falciparum* infection were coded as SAEs.
3. Subject 46 was a 5 year old black male enrolled in Study B2303 who received Coartem 6-dose as a dispersible tablet. His last dose was Sept 7 and the SAE was reported on study day 29 (Oct 3) along with pyrexia. His parasite count was zero and he was diagnosed with meningitis and given benzylpenicillin.

Clonus

Clonus was observed in both the 4-dose and standard tablet 6-dose regimen co-artemether groups, and at higher frequency than that reported with MAS or SP. For the co-artemether 6-dose regimen, there were 11 cases of clonus in total. Ten of the cases were reported in Study A2403 (and all from 1 center) and 1 case from A025.

With respect to the 10 cases of clonus from A2403, 9 of the 10 were detected during routine neurological examinations (predefined in the study protocol) in which specified signs and symptoms were evaluated. Six cases were reported between Day 1 and 3, four between Day 4 and 8. In all cases the investigator described the clonus as suspected to be related to study medication. The intensity of clonus was mild in all but one case which was of moderate intensity (Subject 231). No action was taken in any of the cases and none of the cases were further documented beyond the clinical observation. In 8 of the 10 cases of clonus, no other neurological signs or symptoms were reported. Two subjects (Subjects 122 and 313) had both

clonus and mild hyperreflexia reported, but in the former subject the two nervous system disorder AEs were not concurrent, and with the latter subject, data was missing on the end date for clonus and hyperreflexia so it was impossible to tell if there was any overlap in the two AEs.

The one case of clonus that was not reported from A2403 was subject 74 from study A025. This was a 14 year old male from Thailand with the nervous system AEs clonus, ataxia, headache, nystagmus and tremor reported on study day 1. All were of mild intensity and resolved by day 2 or 3. He also experienced anorexia, diarrhea, dizziness, fatigue, hepatomegaly, pruritis, nausea, nystagmus, abdominal pain, arthralgia, myalgia, palpitations, chills, sleep disorder, vomiting and asthenia on day 1. The neurologic symptoms were not felt to be related to study drug and no action was taken.

There were 3 subjects with the PT “hyperreflexia” and another nervous system AE. Two of these were hyperreflexia and clonus (Subjects 122 and 313 discussed above). The third subject was Subject 229, a 2 year old female with mild hyperreflexia reported from study day 8 to 30, and mild myoclonus from days 15 to 30. Her parasite count was 0 on day 8 and 15, but was 35,337 on day 30. Both nervous system AEs were suspected to be related to study drug.

No cases of clonus or hyperreflexia occurred at the other two centers in Study A2403, or in Study B2303, which was the largest study performed with the 6-dose regimen (899 patients). The significance of these clonus cases is not clear. The Applicant pointed out the difficulties in excluding a possible subclinical cerebral involvement in malaria, and in distinguishing clonus from, for example, muscle contractions due to electrolyte disturbances that might occur in febrile patients.

Results of neurological clinical examinations performed in study B2303 at each visit including baseline reported the following: seven of the 899 patients (0.8%) had abnormalities, most commonly tandem walk and gait abnormal, at baseline; only one patient had any post-baseline abnormalities and this was a patient treated with the dispersible tablet who had gait abnormal and tandem walk at 8 and 24 hours. Both abnormalities were already present at baseline. All reported abnormalities were mild.

Neurological examinations were also performed in Study A2403, and at one site only in both studies A025 and A026. In studies AB/MO2, A023, A028, A2401, neurological findings were recorded as AEs only.

Neurological abnormalities, commonly tandem walk and gait abnormal, clonus, nystagmus, tremor, Romberg test positive, were reported in a limited number of patients at baseline; these symptoms were generally attributed to malaria. Most abnormalities still observed post-baseline were mild and resolved by Day 8.

Conclusions

Based on the analysis to date, which does not include post marketing nervous system events or auditory analysis, there is no strong evidence that the neurohistopathologic effects of artemether

observed in preclinical models results in clinically measureable nervous system AEs in humans. This is based on data from over 1400 co-artemether exposures in adults and 1990 exposures in the pediatric population. Headache and dizziness were the most frequently reported nervous system AEs in both populations, and were likely symptoms of malaria infection. AEs related to balance were reported infrequently, and occurred more with 4-dose than 6-dose exposures. The majority of nervous system AEs were of mild intensity, and case report review of severe AEs and SAEs suggested that the vast majority of these events were likely unrelated to study drug.

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