

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-268

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	4/07/2009
From	Edward M. Cox, MD, MPH
Subject	Office Director Decisional Memo
NDA #	22-268
Applicant Name	Novartis
Date of Submission	6/27/2008
PDUFA Goal Date	December 27, 2008 (priority review)
Proposed Proprietary Name / Established (USAN) Name	Coartem artemether/lumefantrine
Dosage Forms / Strength	tablet artemether 20 mg / lumefantrine 120 mg
Indication	treatment of acute, uncomplicated malaria infections due to <i>Plasmodium falciparum</i> in patients of 5 kg bodyweight and above. Coartem Tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported.
Action:	Approval NDA 22-268

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Background

Coartem is a fixed dose combination tablet comprised of artemether 20 mg / lumefantrine 120 mg that has been developed for the treatment of malaria. Artemether / lumefantrine is approved in over 80 countries around the world and marketed under the trade names Riamet and Coartem. It was first approved in Europe in 1998. Novartis reports that 100 million courses of artemether/lumefantrine have been dispensed to date. Novartis received orphan-drug designation for Coartem for treatment of infections due to *Plasmodium falciparum* or mixed infections including *Plasmodium falciparum* on August 31, 2007.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of Coartem for the treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum*. For a detailed discussion of NDA 22-268, the reader is referred to the individual discipline specific reviews and addenda along with the Cross Discipline Team Leader Review and addendum and the Division Director Review. The Division Director Review provides a detailed description of the overall NDA. This memorandum will focus on selected issues from the application.

Chemistry Manufacturing and Controls (CMC)

Coartem is a fixed dose combination tablet comprised of artemether 20 mg and / lumefantrine 120 mg. Artemether is slightly soluble in water and lumefantrine is insoluble in water and highly lipophilic. The CMC reviewers recommend approval. The status of the manufacturing facilities inspections is acceptable as of March 27, 2009. At the time of the

PDUFA goal date (December 27, 2008) the facilities inspections had yet to be completed and a deficiency had arisen that still needed to be addressed. The outstanding manufacturing facilities inspections and the CMC deficiency that was outstanding in December 2008 have been completed and addressed, respectively. A postmarketing commitment for the development of a dissolution test method for Coartem tablets and postmarketing requirements (PMR) for an in vitro bacterial mutation test and spectral characterization of specified impurities are included in the approval letter.

Pharmacology Toxicology

The recommendation from the Pharmacology and Toxicology Review is that there are no pharmacology toxicology data that preclude the approval of Coartem. Coartem is labeled as Pregnancy Category C. Reproductive toxicology studies showed fetal losses and resorption. The main organs of toxicity for artemether/lumefantrine are the cardiac and nervous system. A study in dogs where artemether was given intramuscularly (IM) for 8 days revealed lesions in the central nervous system (CNS). This finding was not seen in dogs that received artemether orally for 8 days. Systemic plasma concentrations of artemether in dogs following oral administration were lower than that seen with IM dosing. A study in juvenile rats to evaluate neurotoxicity is included among the postmarketing requirements.

Microbiology

The recommendation from the Clinical Microbiology Reviewers is for approval. The activity of artemether, dihydroartemisinin (DHA is an active metabolite of artemether), and lumefantrine were evaluated alone or in combination using in vitro and in vivo animal models of infection. The Clinical Microbiology Reviews also note that the performance characteristics and quality control for the PCR methods used for determination of recrudescence vs. re-infection were not provided and therefore should be interpreted with caution. The issue with quality control and methods is also why only uncorrected parasitological cure rates are presented in the product label. The approval letter includes a PMR to evaluate the potential development of resistance over 5 years to Coartem in malaria endemic countries.

Clinical Pharmacology

The Clinical Pharmacology Reviewer finds that the information submitted in support of Coartem is acceptable. Artemether and lumefantrine are metabolized predominantly by CYP3A4. Artemether also appears to induce its own metabolism through CYP3A4. Lumefantrine inhibits CYP2D6 in vitro and therefore may increase levels of drugs metabolized by CYP2D6. In the product label caution is recommended when combining Coartem with substrates, inhibitors, or inducers of CYP3A4 and substrates of CYP2D6, especially drugs that prolong the QT interval. In addition, several studies are included among the postmarketing requirements in order to further evaluate the potential for drug interactions.

Food enhances the absorption of both artemether and lumefantrine several fold over fasting conditions. Therefore, in clinical studies of Coartem, it was recommended that patients take Coartem with food. The product will be labeled to be taken with food. The label also states that no specific dose adjustment is recommended for patients with mild or moderate hepatic or renal impairment.

Clinical and Statistical

The results of the clinical trials evaluating the safety and efficacy of Coartem are discussed in detail in the Medical Officers' and Statistical Reviews and also in the reviews prepared by the Cross Discipline Team Leader and the Division Director. The reader is referred to their reviews for a detailed discussion of safety and efficacy.

The application included results from a number of clinical trials evaluating the safety and efficacy of Coartem (artemether/lumefantrine) and the components, artemether and lumefantrine, alone, and in combination. The results of these studies demonstrate the efficacy of Coartem (artemether/lumefantrine) as a fixed dose combination product by showing the contribution of the components and showing the efficacy of the combination product in the treatment of acute uncomplicated malaria due to *Plasmodium falciparum* in adult and pediatric patients weighing 5kg or more.

The safety of artemether and lumefantrine was evaluated in over 3000 adult and pediatric subjects, with over 1900 receiving a 6-dose regimen. The most frequently reported adverse events in adults were headache, anorexia, dizziness, and asthenia; the most frequently reported adverse reactions in children were pyrexia, cough, vomiting, anorexia, and headache. The approval letter also includes a PMR to complete an ongoing audiology trial.

The effects of Coartem on the QT interval were evaluated in a thorough QT study. At the therapeutic dose Coartem increased the QT interval (QTcF) by a mean of 7.3msec (90% CI 3.6, 11.0), which is slightly above the 10 msec threshold for the upper bound of the confidence interval specified in ICH E14. Consistent with the recommendation from the Interdisciplinary QT Review Team, the labeling for Coartem will include a statement in the Warnings and Precautions section of the product label regarding effects on prolongation of the QT interval. The Warnings and Precautions section will also include statements about the potential for drug interactions with other QT prolonging drugs, including some CYP2D6 substrates, other antimalarials, and substrates or inhibitors of CYP3A4.

DSI Inspections

The Division of Scientific Investigations performed clinical inspections of six clinical sites and also inspected the applicant. At some sites some deviations from FDA regulations were noted. However, DSI findings note that, in general, the studies appear to have been conducted adequately and that the data from the sites may be used in support of the application. The recommendation from DSI is that the findings from the clinical trial sites did not identify any significant problems that would likely impact upon the reliability of the data. DSI concluded that the data collected and maintained at the applicant's site appeared consistent with that submitted to the agency in NDA 22-268.

Advisory Committee

NDA 22-268 was presented to the Anti-Infective Drugs Advisory Committee on December 3, 2008. The Committee voted Yes 18, No 0 on the question of whether the six-dose regimen of Coartem had been shown to be effective in the treatment of patients with acute uncomplicated *P. falciparum* malaria. The Committee voted Yes 17, No 1, on the question of whether

Coartem had been shown to be safe for the same indication. On the question of whether the data supported the safety and efficacy for the treatment of co-infection with *P. falciparum* and *P. vivax* the Committee voted Yes 9, No 8. Consistent with the recommendations of Advisory Committee, the approval letter includes a PMR to gather additional data in non-immune travelers.

Tropical Disease Priority Review Voucher

Coartem is a new chemical entity, received a priority review, and is indicated for the treatment of *P. falciparum* malaria and therefore qualifies for a tropical disease priority review voucher in accordance with section 524 of the Federal Food, Drug, and Cosmetic Act.

Summary

I have considered the information provided in the reviews of NDA 22-268 and I concur with the recommendations from the Cross Discipline Team Leader, and Division Director that the applicant has provided substantial evidence to support the safety and efficacy of Coartem for the treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum*. The product label describes the risks and benefits of Coartem. As listed in the approval letter, there are a number of postmarketing requirements and a postmarketing commitment for Coartem to further evaluate selected issues for which additional information is warranted postmarketing.

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/s/

Edward Cox
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MEDICAL OFFICER