CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213036Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213036
PDUFA Goal Date	May 26, 2020
OSE RCM #	2019-1721, 2019-1725
Reviewer Name(s)	Brad Moriyama, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	May 24, 2020
Subject	Evaluation of Need for a REMS
Established Name	artesunate
Trade Name	
Name of Applicant	Amivas, LLC
Therapeutic Class	antimalarial agent
Formulation(s)	110 mg vial
Dosing Regimen	artesunate 2.4 mg/kg intravenous bolus at 0 hours, 12 hours, and 24 hours and thereafter once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity artesunate is necessary to ensure the benefits outweigh its risks. Amivas, LLC submitted a NDA 213036 for artesunate with the proposed indication for the initial treatment of severe malaria in adult and pediatric patients. The serious risks associated with artesunate include post-treatment hemolysis, hypersensitivity, and embryo-fetal toxicity in animals. The applicant did not submit a proposed REMS or a risk management plan with this application.

DRM and Division of Anti-Infectives (DAI) agree that a REMS is not necessary to ensure the benefits of artesunate outweigh its risks. The efficacy of artesunate was demonstrated in the SEAQUAMAT study and the supportive AQUAMAT study, in which artesunate was effective for the treatment of severe malaria in adults and children and provided a survival benefit when compared to quinine. The serious risks including post-treatment hemolysis, hypersensitivity, and embryo-fetal toxicity in animals will be communicated in the warnings and precautions section of the label.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] artesunate is necessary to ensure the benefits outweigh its risks. Amivas, LLC submitted a NDA 213036 for artesunate with the proposed indication for the initial treatment of severe malaria in adult and pediatric patients.[1] This application is under review in the Division of Anti-Infectives (DAI). The applicant did not submit a proposed REMS or a risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Artesunate, a NME, is an antimalarial agent. Artesunate is proposed for the initial treatment of severe malaria in adult and pediatric patients. It is supplied as a 110 mg vial for IV injection. The proposed dosing regimen is artesunate 2.4 mg/kg intravenous bolus over 1 to 2 minutes at 0 hours, 12 hours, and 24 hours and thereafter administered once daily until the patient is able to tolerate oral antimalarial therapy.[b] Treatment of severe malaria with artesunate for injection should always be followed by a complete treatment course of an appropriate oral antimalarial regimen. Concomitant therapy with an antimalarial agent such as an 8-aminoquinoline drug is necessary for the treatment of severe malaria due to *Plasmodium vivax* or *Plasmodium ovale.* Artesunate was designated as an orphan product, received fast track designation, and breakthrough therapy.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for artesunate NDA 213036 relevant to this review:

- 03/28/2006: Orphan drug designation granted

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 10/17/2006: Fast track designation granted
- 09/11/2018: Breakthrough therapy designation granted
- 09/26/2019: NDA 213036 submission for the initial treatment of severe malaria in adult and pediatric patients received
- 12/26/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for artesunate

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

The definition of severe malaria, as defined by the CDC for malaria surveillance, includes a case of malaria with one or more manifestations including neurologic symptoms, acute kidney injury, severe anemia, acute respiratory distress syndrome, jaundice, or ≥ 5% parasitemia.[2] The estimated number of cases of malaria worldwide in 2018 was 228 million, with an estimated 405,000 deaths.[3] The number of cases of malaria in the United States and its territories in 2016 was 2078, with the majority of cases imported from other countries.[2,c] Furthermore, the number of cases of severe malaria in the United States and its territories in 2016 was 306, with seven patients dying with severe malaria.[d]

3.2 Description of Current Treatment Options

The CDC guidelines for the treatment of malaria in the United States recommend prompt and aggressive therapy for severe malaria.[4] The CDC guidelines recommend intravenous artesunate for adult and pediatric patients with severe malaria. Intravenous artesunate is currently available from the CDC under an expanded access investigational new drug (IND) protocol for patients with severe malaria and patients with uncomplicated malaria who are unable to take oral medications.[5] Quinidine gluconate injection, an antiarrhythmic and antimalarial agent, was approved by the FDA for the treatment of malaria, but has been discontinued by the manufacturer and is no longer available in the United States.[5,6]

4 Benefit Assessment

The efficacy of artesunate for the treatment of severe malaria was demonstrated in a pivotal study (SEAQUAMAT) and a supportive study (AQUAMAT).[1,7] SEAQUAMAT was an international, multicenter, randomized, open label, active-controlled trial. Patients in this study were enrolled in Bangladesh, India,

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Indonesia and Myanmar and were adults or children > 2 years old. The primary efficacy endpoint was in-hospital mortality. Patients (N=1461) were randomized to artesunate 2.4 mg/kg IV at 0, 12, and 24 hours and then every 24 hours until the patient could tolerate oral medication (N= 730) and quinine 20 mg/kg IV, then 10 mg/kg IV three times daily until oral therapy could be started (N= 731). The primary efficacy endpoint for in-hospital mortality was 13% in the artesunate group and 21% in the quinine group (odds ratio 0.59, 95% confidence interval 0.44 to 0.79).

The FDA clinical reviewer concluded that artesunate was effective for the treatment of severe malaria in adults and children and provides a survival benefit when compared to quinine.[7,e]

5 Risk Assessment & Safe-Use Conditions[f]

The safety of artesunate was evaluated in a clinical trial for the treatment of severe malaria (SEAQUAMAT) and an open label study for the treatment of severe malaria (CDC-060).[1,7] The safety of artesunate was also evaluated in a supportive clinical trial (AQUAMAT). In the safety population from SEAQUAMAT, 730 patients received artesunate and 730 patients received quinine. Common adverse reactions reported with artesunate included acute renal failure requiring dialysis, hemoglobinuria, and jaundice. CDC-060 was a retrospective analysis of an IND treatment study of artesunate in adults and children with severe malaria. In the safety population from CDC-060, 102 patients received artesunate. Common adverse reactions reported with artesunate included anemia, transaminase increase, thrombocytopenia, hyperbilirubinemia, acute renal failure, leukocytosis, acute respiratory distress syndrome, lymphopenia, neutropenia, disseminated intravascular coagulation, elevated creatinine, pneumonia, pulmonary edema, and diarrhea.

The serious risks[g] associated with artesunate which include post-treatment hemolysis, hypersensitivity, and embryo-fetal toxicity in animals are summarized in the sections below.

5.1 POST-TREATMENT HEMOLYSIS

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Post-treatment hemolytic anemia has been reported with artesunate. The proposed label recommends to monitor patients for 4 weeks after artesunate treatment for evidence of hemolytic anemia. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2 HYPERSENSITIVITY

Anaphylaxis has been reported with artesunate including artesunate for injection. Artesunate is contraindicated in patients with known serious hypersensitivity to artesunate such as anaphylaxis. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3 EMBRYO-FETAL TOXICITY IN ANIMALS

Intravenous artesunate has been reported to cause embrolethality in animal studies in rats and oral artesunate has been reported to cause dose-dependent increase in embryolethality and fetal malformations in animal studies in rats, rabbits, and monkeys. A Division of Pediatric and Maternal Health (DPMH) consult indicated that a risk of congenital malformations, miscarriage or other adverse pregnancy or fetal outcomes have not been identified with IV and oral artesunate and other artemisinin drugs in humans.[8] However, as limited clinical data is available with intravenous artesunate in pregnancy in humans, DPMH recommended a PMR for a single-arm pregnancy safety study. The proposed label states that there are serious risks to the mother and fetus associated with untreated malaria during pregnancy; delaying treatment of severe malaria in pregnancy may result in serious morbidity and mortality to the mother and fetus. If approved, this risk will be communicated in the warnings and precautions section of the label.

During the review of the artesunate NDA 213036 proposed label, this reviewer asked if (b) (4) (b) (4) should be included in the proposed label.

6 Expected Postmarket Use

If approved, artesunate will primarily be used in inpatient settings. The likely prescribers will be critical care medicine practitioners and infectious diseases specialists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for artesunate beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of artesunate on the basis of the efficacy and safety information currently available. Severe malaria is a medical emergency, which requires aggressive treatment. Currently, there are no FDA approved intravenous drugs for the treatment of severe malaria and intravenous artesunate is available from the CDC under an IND protocol. The efficacy of artesunate

was demonstrated in the SEAQUAMAT study and the supportive AQUAMAT study, in which artesunate was effective for the treatment of severe malaria in adults and children and provided a survival benefit when compared to quinine. The serious risks associated with artesunate of post-treatment hemolysis, hypersensitivity, and embryo-fetal toxicity in animals will be communicated in the warnings and precautions section of the label.

The estimated number of cases of malaria worldwide in 2018 was 228 million, with an estimated 405,000 deaths. The number of cases of malaria in the United States and its territories in 2016 was 2078, with the majority of cases imported from other countries. Furthermore, the number of cases of severe malaria in the United States and its territories in 2016 was 306, with seven patients dying with severe malaria. The likely prescribers will be critical care medicine practitioners and infectious diseases specialists who should be knowledgeable about managing the serious adverse events reported with artesunate. If approved, based on the efficacy and risks associated with artesunate for the initial treatment of severe malaria in adult and pediatric patients, the DRM and DAI agree that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for artesunate to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Proposed prescribing information for artesunate NDA 213036 as currently edited by FDA, May 17, 2020.

[2] Mace KE, Arguin PM, Lucchi NW, Tan KR. Malaria Surveillance – United States, 2016. MMWR Surveill Summ 2019;68(No. 5):1-35.

[3] World malaria report 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

[4] Centers for Disease Control and Prevention. Treatment of Malaria: Guidelines for Clinicians (United States). Accessed April 27, 2020. (https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html)

[5] Centers for Disease Control and Prevention. Intravenous Artesunate for Treatment of Severe Malaria in the United States. Accessed April 27, 2020. (https://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html)

[6] Krey RA, Travassos MA. Severe Malaria Treatment in the United States at the Precipice. Ann Intern Med 2019;171(5):362-363.

[7] Artesunate NDA 213036 multi-disciplinary review and evaluation. Accessed May 19, 2020.

[8] Division of Pediatric and Maternal Health consult to NDA 213036. March 2, 2020.

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/s/

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