Drug Monograph

Drug Name: **Artesunate for Injection Vial**
Drug Class: **Anti-infectives: Antimalarial**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Artesunate for Injection is available as 110 mg of Artesunate powder in a single-dose vial for constitution with the supplied sterile diluent.
Manufacturer:	Distributed by: Amivas LLC, Wilmington, DE 19801.
Summary of Findings:	The safety and efficacy of IV Artesunate for the treatment of severe malaria was primarily evaluated in a randomized controlled trial in Asia (Trial 1) and a supportive published randomized controlled trial in Africa (Trial 2). Both studies compared Artesunate at 2.4 mg/kg on admission, at 12 hours, at 24 hours, and then daily to quinine at a 20 mg/kg loading dose, then 10 mg/kg three times daily. Both regimens were continued until oral therapy was tolerated. The primary endpoint was in-hospital mortality. Trial 1 showed a relative risk reduction of 34.7% (*p=0.0002*) for the Artesunate arm. Trial 2 showed a relative risk reduction of 22.5% (*p=0.0022*) for Artesunate compared to quinine. Both studies concluded that Artesunate should become the treatment of choice over quinine for severe malaria.
Status Recommendation:	☐ Clinical Edit ☒ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

According to the Centers for Disease Control and Prevention (CDC), there were approximately 229 million cases of malaria worldwide and 409,000 deaths in 2019. The majority of these numbers occurred in children in the African region. Most of the cases in the United States are in travelers and immigrants returning from sub-Saharan Africa and South Asia, and amount to about 2,000 cases per year. Malaria is a serious and sometimes fatal disease caused by a parasite belonging to the genus *Plasmodium*. There are five species that can infect humans: *P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi*. Infection in humans is usually the result of being bitten by an infective female Anopheles mosquito. A mosquito becomes infected through a previous blood meal taken from an infected person. In humans, the parasites grow and multiply first in the liver cells and then in the red blood cells (RBCs). Successive broods of parasites grow inside the RBCs and destroy them, releasing daughter parasites (merozoites) that can continue the disease process by invading other RBCs. Because malaria is a blood-borne infection, it can also be the result of a blood transfusion, organ transplant, or the shared use of needles or syringes contaminated with blood. Signs and symptoms of malaria include high fevers, shaking chills, and flu-like symptoms, and left untreated can be deadly. Children under 5 years old are the most vulnerable to serious malaria infections and account for 67% of the malaria deaths worldwide. Both the CDC and the World Health Organization (WHO) have programs designed to prevent, treat and track malaria infections.

Dosage Form [3]

Artesunate for Injection is available as 110 mg of Artesunate powder in a single-dose vial for constitution with the supplied sterile diluent.

Manufacturer [3]

Distributed by: Amivas LLC, Wilmington, DE 19801.

Indication(s) [3]

Artesunate for Injection is an antimalarial indicated for the initial treatment of severe malaria in adult and pediatric patients. Treatment of severe malaria with Artesunate for Injection should always be followed by a complete treatment course of an appropriate oral antimalarial regimen.
Limitations of Use: Artesunate for Injection does not treat the hypnozoite liver stage forms of Plasmodium and will therefore not prevent relapses of malaria due to *Plasmodium vivax* or *Plasmodium ovale*. Concomitant therapy with an antimalarial agent such as an 8-aminoquinoline drug is necessary for the treatment of severe malaria due to *P. vivax* or *P. ovale*.

Clinical Efficacy [3,4,5,6] (mechanism of action/pharmacology, comparative efficacy)

Artesunate is rapidly metabolized into an active metabolite dihydroartemisinin (DHA). Artesunate and DHA, like other artemisinins contain an endoperoxide bridge that is activated by heme iron leading to oxidative stress, inhibition of protein and nucleic acid synthesis, ultrastructural changes as well as a decrease in parasite growth and survival. Both Artesunate and DHA are active against the different asexual form of the *Plasmodium* parasites and clear parasitemia within 48 to 72 hours. Artesunate and DHA are active against the blood-stage asexual parasites and gametocytes of *Plasmodium* species including the chloroquine resistant strains. However, Artesunate and DHA are not active against the hypnozoite liver stage forms of *P. vivax* and *P. ovale*.

Pharmacokinetics: (N=14)

	Artesunate (AS)	**Dihydroartemisinin (DHA)**
Absorption (C_{max})	3.3 mcg/mL (1.0-164)	3.1 mcg/mL (1.7-9.5)
In Vitro Metabolism-Primary Pathway (Metabolite)	Blood Esterases (DHA)	Glucuronidation (α-DHA-β-glucuronide)
Excretion (Urine)	N/A	N/A
Half-life (hours)	0.3 (0.1-1.8)	1.3 (0.9-2.9)

Clinical Trials Experience

STUDY 1 DESIGN (SEAQUAMAT)	International randomized, open-label, multicenter trial conducted in Bangladesh, India, Indonesia, and Myanmar (N=1461)
INCLUSION CRITERIA	• Hospitalized patients with severe malaria (only 1382 patients had a confirmatory blood smear) • Age >2 years
EXCLUSION CRITERIA	• Convincing history of full treatment with quinine or an artemisinin derivative for more than 24 hours before admission • Hypersensitivity to artemisinin derivatives or quinine
TREATMENT REGIMEN	Patients were treated with Artesunate or quinine. Artesunate was administered at 2.4 mg/kg IV at 0, 12, and 24 hours and then every 24 hours until the patient could tolerate oral medication. Quinine was given IV at 20 mg/kg over 4 hours, followed by 10 mg/kg over 2 to 8 hours, 3 times daily until oral therapy could be started.
RESULTS	**In-hospital Mortality in Patients Treated for Severe Malaria in Trial 1, All Randomized Patients**

	Artesunate (N=730)	**Quinine (N=731)[2]**	**Odds Ratio (95% CI)[1]**
In-hospital mortality	96 (13%)	150 (21%)	0.59 (0.44, 0.79)

[1] The odds ratio and 95% CI (confidence interval) were calculated using the Cochran-Mantel-Haenszel approach adjusted by study site.
[2] A single patient randomized to quinine arm did not receive any doses of the study drug.

The in-hospital mortality rate in the Artesunate group (13%) was significantly lower than the rate in the quinine group (21%). The relative risk reduction (RRR) was 34.7% (p=0.0002) and the number needed to treat (NNT) was 11.1-20.2 based on the study country.

SAFETY	Discussed in the Adverse Effects section below.

<table>
<tr><td>STUDY 2 DESIGN (AQUAMAT)</td><td>International randomized, open-label, multicenter trial conducted in nine African countries (N=5425)</td></tr>
<tr><td>INCLUSION CRITERIA</td><td>• Hospitalized patients with severe malaria (positive rapid diagnostic test for P. falciparum)
• <15 years old</td></tr>
<tr><td>EXCLUSION CRITERIA</td><td>• Convincing history of full treatment with parenteral quinine or an artemisinin derivative for more than 24 hours before admission</td></tr>
<tr><td>TREATMENT REGIMEN</td><td>Patients were treated with Artesunate or quinine. Artesunate was administered at 2.4 mg/kg IV or IM (not an approved route of administration) on admission, at 12 hours, 24 hours and then every 24 hours until the patient could tolerate oral medication. Quinine was given IV or IM at 20 mg/kg, followed by 10 mg/kg three times daily until oral therapy could be started.</td></tr>
<tr><td>RESULTS</td><td>In-hospital Mortality in Patients Treated for Severe Malaria in Trial 2, All Randomized Patients
<table>
<tr><th></th><th>Artesunate (N=2712)</th><th>Quinine (N=2713)[2]</th><th>Odds Ratio (95% CI)[1]</th></tr>
<tr><td>In-hospital mortality</td><td>230 (8.5%)</td><td>297 (10.9%)</td><td>0.75 (0.63, 0.90)</td></tr>
</table>
[1] The odds ratio and 95% CI (confidence interval) were calculated using the Cochran-Mantel-Haenszel approach adjusted by study site.
[2] A single patient randomized to quinine arm did not receive any doses of the study drug.
The in-hospital mortality rate in the Artesunate group (8.5%) was significantly lower than the rate in the quinine group (10.9%). The RRR was 22.5% (p=0.0022) and the NNT was 41.</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
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Contraindications [3,4]

- Serious hypersensitivity to Artesunate, such as anaphylaxis.

Warnings and Precautions [3,4]

- **Post-treatment Hemolysis:** Cases of post-treatment hemolytic anemia severe enough to require transfusion have been reported. Monitor patients for 4 weeks after treatment for evidence of hemolytic anemia.
- **Hypersensitivity:** Serious hypersensitivity reactions including anaphylaxis have been reported. Discontinue if signs of serious hypersensitivity occur.

Adverse Effects [3,4]

Most common, ≥2 %	Artesunate (N=730) n (%)	Quinine (N=730)[1] n (%)
Acute renal failure requiring dialysis[2]	65 (8.9%)	53 (7.3%)
Hemoglobinuria	49 (6.7%)	33 (4.5%)
Jaundice	17 (2.3%)	14 (1.9%)

[1] In Trial 1, 1 patient randomized to the quinine arm did not receive any doses of the study drug.
[2] Includes the terms: dialysis, hemodialysis, and peritoneal dialysis.

Drug Interactions [3,4]

- Nevirapine or ritonavir antiretrovirals: If used concomitantly, monitor for possible reduced antimalarial efficacy.
- Strong UGT inducers (e.g., rifampin, carbamazepine, and phenytoin): If used concomitantly, monitor for possible reduced antimalarial efficacy.

Dosage and Administration [3,4]

- The recommended dosage of Artesunate for injection is 2.4 mg/kg administered intravenously at 0 hours, 12 hours, 24 hours, and thereafter administered once daily until the patient is able to tolerate oral antimalarial therapy.
- Administer constituted Artesunate for injection intravenously as a slow bolus over 1 minute to 2 minutes.
- Do NOT administer Artesunate for injection via continuous intravenous infusion.
- Administer Artesunate for injection with an antimalarial agent that is active against the hypnozoite liver stage forms of *Plasmodium*, such as an 8-aminoquinolone drug, to patients with severe malaria due to *P. vivax* or *P. ovale*.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Vial
Artesunate	-----	Amivas	2.4 mg/kg IV at 0 hours, 12 hours, and 24 hours, and once daily thereafter	$9,960 (70 kg person would need 2 vials per dose)

** Wholesale Acquisition Cost

Conclusion

Malaria, or infection with the *Plasmodium* parasite, is a potentially deadly illness with an estimated 2,000 cases in the U.S. each year. The parasites grow and multiply first in the liver cells and then in the red blood cells (RBCs). Artesunate and DHA are active against the blood-stage asexual parasites and gametocytes of Plasmodium species including the chloroquine resistant strains. However, Artesunate and DHA are not active against the hypnozoite liver stage forms of *P. vivax* and *P. ovale. T*herefore, it must be administered with an antimalarial agent that is active against the hypnozoite liver stage forms of *Plasmodium*, such as an 8-aminoquinolone drug. In 2006, the WHO recommended Artesunate as first choice for treatment of severe malaria and in 2019, the CDC declared it as first-line for treatment of severe malaria in the U.S. The FDA did not approve Artesunate in the U.S. until 2020. Rapid and accurate diagnosis of malaria is critical to the appropriate treatment of those infected and to prevent the spread of infection in the community. Currently, the WHO and the CDC recommend Artesunate as first-line treatment for severe malaria.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) Centers for Disease Control and Prevention. Malaria. https://www.cdc.gov/parasites/malaria/index.html. Accessed November 3, 2021.
2) World Health Organization. Malaria. https://www.who.int/news-room/fact-sheets/detail/malaria. Accessed November 3, 2021.
3) Artesunate [package insert]. Wilmington, DE: Amivas; May 2020.
4) IPD Analytics. Artesunate New Drug Review. https://secure.ipdanalytics.com/. Accessed November 3, 2021.
5) South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet.

2005;366(9487):717-725. doi:10.1016/S0140-6736(05)67176-0
6) Dondorp AM, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010;376(9753):1647-1657. doi:10.1016/S0140-6736(10)61924-1

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