Artesunate (Artesunate for Injection™, Amivas, LLC) **June 2021**
Non-Formulary

Criteria for Formulary Consideration of Artesunate

Efficacy[14,15,17,18]
Artesunate (Artesunate for Injection™) is FDA approved for initial treatment of severe malaria in children and adults. The CDC and WHO guidelines currently recommend IV artesunate as first-line therapy for this indication. Clinical trials have demonstrated lower in-hospital mortality when artesunate is used compared to the previous standard of care, parenteral quinine, which is no longer marketed for use in the United States.

Safety[12,13]
The most common adverse effects of artesunate include acute renal failure, hemoglobinuria, jaundice, and neurological side effects (including balance impairment, confusion, tremor, and weakness). Rare cases of anaphylaxis and hemolytic anemia have also been reported.

Uniqueness[11,12]
Artesunate (Artesunate for Injection™) is the only FDA approved drug for treatment of severe malaria in the United States.

Cost
Artesunate is available for purchase from Cardinal in 220mg and 440mg quantities

- 220mg cost: $9,960
- 440mg cost: $19,920

Artesunate therapy estimated cost by weight of patient

	20 kg	**70 kg**	**100 kg**
Dose	48 mg (1 vial/110mg used)	168 mg (2 vials/220mg used)	240 mg (3 vials/330mg used)
Cost per dose	$4,980	$9,960	$14,940
Cost for minimum course (24 hrs)	$14,940	$29,880	$44,820
Cost for maximum course (7 days)	$44,820	$89,640	$134,460

Recommendations

Add to formulary with restriction to the infectious diseases services

The authors of this document have no financial relationship with pharmaceutical companies, biomedical device manufacturers, or distributors or others whose products or services may be considered related to the subject matter within.

Introduction

It is estimated that that there were approximately 229 million cases of malaria, leading to approximately 409,000 deaths worldwide in 2019. In the United States, approximately 2000 cases (~300 severe) are diagnosed annually, occurring most frequently in travelers or immigrants from endemic areas, such as sub-Saharan Africa, Latin America, and southeast Asia.[1-3]

Malaria is a serious and potentially fatal parasitic infection of erythrocytes typically transmitted to and between humans through infected female *Anopheles* mosquitos. It can also be transmitted through blood transfusion or organ transplant from infected donors, shared needles contaminated with infected blood, or from mother to infant during birth. Species of malaria parasites causing disease in humans include *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. Malaria due to *P. falciparum* is the most likely to result in severe or fatal illness.[2,4-6]

Malaria is a cyclical infection which starts when female *Anopheles* mosquitos inject *Plasmodium* sporozoites into the human bloodstream. Sporozoites infect human hepatocytes (liver stage) and mature into schizonts, which invade erythrocytes (blood stage). Schizonts grow and multiply within the erythrocytes, eventually causing cell lysis and release of merozoites (daughter parasites) into the bloodstream, which then infect new erythrocytes. Blood stage parasites exist in asexual and sexual (gametocyte) forms. When gametocytes are ingested by female *Anopheles* mosquitos, they mate and multiply within the gut of the mosquito, forming new sporozoites which migrate to the salivary glands and are transmitted to another human host. Two species, *P. vivax* and *P. ovale*, have a dormant form known as a hypnozoite, which can persist in the liver for weeks to years if untreated.[6]

Clinical symptoms of malaria are caused by blood stage *Plasmodium* parasites. As the parasites develop inside infected erythrocytes, pro-inflammatory molecules are produced, which are released into the bloodstream along with merozoites when the infected cells lyse, leading to cytokine release. Symptoms of malaria are flu-like in nature, including high fevers, rigors, fatigue, and myalgias, as well as gastrointestinal symptoms, such as nausea, vomiting, and diarrhea. Severe cases can lead to severe anemia, jaundice, acute renal failure, respiratory distress, shock, seizures, coma, or death. Onset of symptoms is typically 1-4 weeks post-infection; however, malaria due to *P. vivax* or *P. ovale* can cause relapsing infection up to 4 years later due to reactivation of liver hypnozoites if not treated appropriately.[2,4-6,8]

When malaria is suspected clinically, the gold standard laboratory confirmation is microscopic examination of a thick and thin blood smear to visually detect malaria parasites, differentiate species, and determine parasitemia burden. Rapid diagnostic tests are also available. Once diagnosed, treatment for malaria should be initiated. Preferred therapy depends on severity of infection, which is classified as uncomplicated or severe, as well as *Plasmodium* species, geographic area from which infection was acquired, and previous use of antimalarial agents. In patients with uncomplicated malaria, oral therapy can be safely utilized. In patients with severe malaria, initial treatment with IV therapy is recommended.[7-9]

Historically, first-line therapy for severe malaria was parenteral quinine; however, artesunate, a semi-synthetic derivative of artemisinin, has been shown to be safer and more effective than quinine in clinical trials, and quinine was removed from the market in March 2019. Artesunate, is now recommended as first-line therapy for treatment of severe malaria. Previously, IV artesunate was only available from the CDC through an expanded-use investigational new drug (IND) protocol. Artesunate (Artesunate for Injection™) was FDA approved in May 2020 for the treatment of severe malaria and is now commercially available.[8-15]

Pharmacokinetics[12,13]

Table 1: Pharmacokinetic properties of artesunate and active metabolite, dihydroartemisinin (DHA)

PK Parameter	Artesunate	DHA
Peak plasma concentration	3.3 mcg/mL	3.1 mcg/mL (reached within 15 min of IV administration)
AUC (steady state)	0.7 mg*hr/L	3.5 mg*hr/L
Volume of distribution (steady state)	68.5 L	59.7 L
Protein binding	~93%	~93%
Metabolism	Plasma esterases	Glucuronidation
Elimination half-life	0.3 hrs	1.3 hrs
Excretion/Clearance	Urine; 180 L/hr	Urine; 32.3 L/hr

Pediatrics: Steady state DHA AUC has been found to be similar or greater than that achieved in adults; no dose adjustments required for age
Pregnancy: Peak plasma concentrations and AUC of artesunate and DHA have been found to be similar between pregnant and post-partum patients; no dose adjustments required in pregnancy

Pharmacodynamics[12]
The exposure-response relationships for artesunate and DHA have not yet been established. Parasitemia is generally cleared within 48-72 hrs of treatment initiation.

Pharmacology[12,13]
Artesunate is an artemisinin derivative, schizonticidal antimalarial agent. It is administered as a prodrug which is rapidly converted to dihydroartemisinin (DHA), an active metabolite. Artesunate and DHA are activated by binding heme iron in infected erythrocytes, which leads to oxidative stress and ultimately allows inhibition of protein and nucleic acid synthesis, which inhibits growth and survival of *Plasmodium* parasites. Artesunate is active against blood stage parasites (including gametocytes and asexual parasites) but not against liver stage hypnozoite forms of *Plasmodium vivax* or *Plasmodium ovale*.

FDA Approved Indications[12]
Approved May 2020 for initial treatment of severe malaria in adults and children

Clinical Trials[14-18]

Table 2: Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial (SEAQUAMAT)[14]

Study Design	Methods	Results	Conclusions/Comments
Dondorp A. et al, Lancet 2005 Multicenter, open-label, randomized controlled trial (Bangladesh, Myanmar, India, Indonesia) Patients randomized to receive IV artesunate 2.4 mg/kg at 0, 12, and 24 hrs, then daily (n=730) or IV quinine 20 mg/kg loading dose, then 10 mg/kg TID (n=731) • Transitioned to oral therapy when possible to complete treatment Followed through in-hospital death or well-discharge	Inclusion Criteria • Age >2yrs • Positive *Plasmodium falciparum* histidine rich protein 2 (HPR2) blood antigen test • Severe malaria Exclusion Criteria • Full treatment with quinine or >24hrs of artemisinin derivative prior to admission • Allergy to trial drugs Statistical analysis • 80% power to detect 33% mortality reduction • Intention to treat and per-protocol analyses • Comparisons stratified by site	Primary Efficacy Variable Results • In-hospital mortality 15% in artestunate group vs 22% in quinine group (RR = 0.69, 95% CI 0.54-0.83) ○ Per-protocol: RR = 0.69, 0.55-0.85) ○ ARR 5-9%, NNT 11-20 Secondary Efficacy Variable Results • Combined in-hospital mortality and neurological sequelae 16% in artesunate group vs 23% in quinine group (RR 0.7, 0.57-0.86) • No difference between groups in times to discharge, speak, eat, sit • No difference in convulsions, shock, dialysis, mechanical ventilation, or vasopressor requirements between groups Adverse Events • Excess hypoglycemia in quinine group vs artesunate (RR 3.2, 95% CI 1.3-7.8) • No other serious adverse effects attributed to therapy	Author's Conclusion: artesunate significantly reduces mortality compared to quinine when used as treatment for severe malaria and was associated with fewer adverse events Comments: no data in children <2 yrs, few <6 yrs (n=89), carried out in areas of relatively low transmission

Table 3: Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial[15]

Study Design	Methods	Results	Conclusions/Comments
Dondorp A. et al, Lancet 2010 Multicenter, open-label, randomized controlled trial (11 centers, 9 African countries) Patients randomized to IV or IM artesunate 2.4 mg/kg at 0, 12, and 24 hrs, then daily (n=2712) or IV or IM quinine 20 mg/kg loading dose, then 10 mg/kg TID (n=2713) • Transitioned to oral therapy when possible to complete treatment Study period: October 3, 2005-July 14, 2010; patients followed until full recovery, up to 12 months	Inclusion Criteria • Age <15 yrs • Positive *Plasmodium falciparum* lactate dehydrogenase test Exclusion Criteria • Full treatment with quinine or >24hrs of artemisinin derivative prior to admission Statistical analysis, power, etc • 80% power to detect 25% mortality reduction • Intention to treat and per-protocol analyses • Comparisons stratified by site • Meta-analysis of RCTs comparing artesunate vs quinine performed	Primary Efficacy Variable Results • In-hospital mortality 8.5% in artesunate group vs 10.9% in quinine group (OR stratified by site 0.75, 95% CI 0.63-0.90; RRR 22.5%, 95% CI 8.1-36.9) ○ NNT = 41 ○ Per-protocol OR 0.78, 0.64-0.94) Secondary Efficacy Variable Results • No difference in persistent neurological sequalae at 28 days between groups • Coma, convulsions, and worsening of coma score occurred more often in quinine group vs artesunate group • No difference in time to eat, sit, discharge • Meta-analysis comparing artesunate vs quinine in severe malaria (N>7000): overall mortality OR 0.69 (0.57-0.84) Adverse Events • More hypoglycemia in quinine group vs artesunate group (OR 0.63, 0.43-0.91) • No serious adverse events attributed to artesunate	Author's Conclusion: artesunate is safe and significantly reduces mortality compared to quinine in patients treated for severe malaria and should be first-line therapy worldwide Comments: provided evidence of mortality benefit for children treated with artesunate; contributed meta-analysis showing survival benefit in all age groups with artesunate vs quinine

Table 4: Assessment of parasite clearance following treatment of severe malaria with intravenous artesunate in Ugandan children enrolled in a randomized controlled clinical trial[16]

Study Design	Methods	Results	Conclusions/Comments
Byakika-Kibwika P. et al, Malar J 2018 Randomized clinical trial 150 patients enrolled, all received IV artesunate 2.4 mg/kg (AS) at 0, 12, and 24hrs, then were randomized to receive oral artemether-lumefantrine (AL) (n=79), or dihydroartemisinin-piperaquine (DP) (n=71) Patients were followed for 42 days	Inclusion Criteria • Age ≥6 months • Fever • Positive thick blood smear for malaria • Severe malaria Exclusion Criteria • Concomitant febrile illness • Allergy to study drugs • Resident more than 20 km from the hospital and therefore could not return for follow-up visits • Treatment with effective antimalarial within 24 hours prior to admission Statistical analysis, power, etc • Parasite clearance estimated using parasite clearance estimator from WWARN (World Wide Anti-Malarial Resistance Network) • Non-normally distributed continuous variables: Wilcoxon test • Categorical variables: Chi-square test	Efficacy Results • All able to take oral therapy within 24 hrs • Median days to parasite clearance (PCT) = 2 days (IQR 1-2) • Median clearance half-life = 2.15 hrs (IQR 1.64-2.61) Table I: Time to clear 50, 90, 95, 99% of parasites Parasite clearance (PCT) / Time median (IQR) hours 50% / 4.8 (3.61, 7.10) 90% / 10.20 (8.47, 12.05) 95% / 12.48 (10.57, 14.75) 99% / 17.55 (14.66, 20.60) Adverse Events • No significant adverse events noted	Author's Conclusion: • IV artesunate demonstrated parasitemia clearance within 24-48h, resistance not noted Comments: Most patients <20 kg in study; parasitemia clearance achieved with 2.4 mg/kg dose

	• Risk of treatment failure: Kaplan-Meier survival method and compared using the Log Rank test • P value <0.05 significant		

Table 5: Artesunate to treat severe malaria in travellers: review of efficacy and safety and practical implications[17]

Study Design	Methods	Results	Conclusions/Comments
Roussel C. et al, J Travel Med. 2017 Systematic review on artesunate (AS) use in non-endemic areas Studies included (N=624): • 12 retrospective studies • 1 prospective study • 7 case reports Intervention or treatment • IV AS as first or second line therapy alone or as part of combination therapy • One study used rectal AS • Mostly severe malaria (13 patients uncomplicated) When described, duration of follow-up ranged from 7 days-6 months (unknown in 10 studies)	Literature search (July 2016): Pubmed/Medline and Web of Science Search Criteria • Key word: "AS" and "travellers" or "imported malaria" or "anaemia" or "haemolysis". • Clinical reports in English or French were selected based on PRISMA guidelines	Efficacy • Mortality in travelers treated with AS 4% (23/574); none treatment-related Safety • Data available for 465 patients • Overall, 27.7% of patients reported ≥1adverse event o Most malaria related o 6% considered possibly related to AS (n=28, see Table I below) Table I: Adverse Events Elevation of liver enzymes: 8 (1.7%) Neurological syndromes: 5 (1%) Renal dysfunction: 3 (0.6%) Cutaneous: 3 (0.6%) Cardiac*: 3 (0.6%) Severe arterial ischemia: 1 (0.2%) Hypertension: 1 (0.2%) Hyperkalemia: 1 (0.2%) Early hemolysis: 1 (0.2%) Non-specified minor adverse events: 2(0.4%) *QTc prolongation, bradycardia • Post-AS delayed hemolysis (PADH) occurred in ~15% of patients; ~50% required transfusion	Author's Conclusion: • AS treatment in travelers with severe malaria in non-endemic areas is highly efficacious and reasonably safe • Weekly follow-up of hematological parameters for 1 month post-treatment is supported by the relatively high frequency of PADH Comments: • While RCT is not available, this systemic review is a valuable report to support the use of AS in travelers. • This review includes studies from different countries and may have a relatively good generalizability.

Table 6: Artesunate versus quinine for treating severe malaria[18]

<table>
<tr><th>Study Design</th><th>Methods</th><th>Results</th><th>Conclusions/Comments</th></tr>
<tr>
<td>Sinclair D. et al, Cochrane Database Syst Rev. 2012

Systemic review and meta-analysis

8 trials enrolling 1664 adults and 5765 children included (Asia, Africa)

Intervention or treatment
• Artesunate: intravenous, intramuscular, or rectal
• Quinine (comparison): intravenous or intramuscular

One trial followed patients for 3 weeks after hospital discharge. One other trial followed patients with neurological sequelae for 28 days. Other trials did not report length of follow-up.</td>
<td>Literature search: Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library), MEDLINE, EMBASE, LILACS, ISI Web of Science, the metaRegister of Controlled trials (mRCT), conference proceedings, reference lists of articles to November 2010.

Inclusion Criteria
• Randomized controlled trials
• Artesunate versus quinine
• Adults and children with severe malaria

Exclusion Criteria
16 trials that did not meet inclusion criteria were excluded

Statistical analysis
• Risk ratio (RR) for dichotomous data
• Mean difference (MD) for continuous data
• Estimates presented with 95% confidence intervals (CI)
• Heterogeneity: forest plots; Chi-square test (P<0.10 considered statistically significant); I^2 statistic (I^2 value of 50% used to denote moderate levels of heterogeneity)
• Reporting biases: funnel plots
• Sensitivity analysis</td>
<td>Primary outcome: all-cause death
• Adults: Artesunate treatment reduced the risk of death compared to quinine (RR 0.61, 95% CI 0.50-0.75; 1664 participants, 5 trials).
• Children: Artesunate treatment reduced the risk of death compared to quinine (RR 0.76, 95% CI 0.65-0.90; 5765 participants, 4 trials).
• Mortality reduction consistent across all included trials

Secondary outcomes:
Neurological sequelae:
• Treatment with artesunate compared to quinine was associated with increased incidence of neurological sequelae at the time of hospital discharge (RR 1.41, 95% CI 1.05-1.88; 6422 participants, 3 trials).
○ Incidence in adults is low (<1%); difference between groups not statistically significant
○ One study in children showed 52.7% fully recovered at 28 days; difference not significant between groups
Coma recovery time:
• Unclear due to incomplete report, skewed data, or inconsistent results
Time to hospital discharge:
• No difference between groups
Fever clearance time:
• No difference between groups
Parasite clearance time (PCT):
• Artesunate superior to quinine at reducing the mean PCT:
Table I: Artesunate versus quinine at reducing the mean PCT
<table>
<tr><td>Mean 50% PCT</td><td>MD -8.14 hrs, 95% CI -11.55 to -4.73; 292 participants, 3 trials</td></tr>
<tr><td>Mean 90% PCT</td><td>MD -18.50 hrs, 95% CI -24.13 to -12.87; 61 patients; 1 trial</td></tr>
<tr><td>Mean 95% PCT</td><td>MD -10.69 hrs, 95% CI -20.27 to -1.10, 231 patients; 2 trials</td></tr>
<tr><td>Mean 100% PCT</td><td>MD -9.77hrs 95% CI -18.11 to -1.44, 419 patients; 4 trials</td></tr>
</table>
Adverse Events:
• No trial reported discontinuation of medication
• All adverse effects reported could be attributable to malaria except hypoglycemia and tinnitus (more common with quinine (RR for artesunate vs quinine 0.55, 95% 0.41 to 0.74; 7137 participants, 4 trials)</td>
<td>Author's Conclusion:
• Parenteral artesunate is superior to quinine for the treatment of severe malaria in both adults and children in different regions of the world.

Comments:
• This review includes studies from different geographic regions and may have a relatively good generalizability.
• The majority of the data is from large multicenter trials and has high quality.</td>
</tr>
</table>

Guidelines/Guidance on Place in Therapy[8-10]

CDC guideline[8,10]:

- IV artesunate is first-line for treatment of severe malaria in the United States (regardless of *Plasmodium* species*)
    - Severe malaria = at least one of the following:
        - Neurologic dysfunction (impaired consciousness, coma, seizures)
        - Severe anemia (Hgb <7 g/dL)
        - Shock
        - Acidosis
        - Disseminated intravascular coagulation (DIC)
        - Organ dysfunction (acute kidney injury, pulmonary edema or acute respiratory distress syndrome, jaundice + one other sign)
        - Blood parasite density ≥5%

  *If infection with *P. vivax* or *P. ovale*, addition of anti-relapse treatment is required with agent active against liver hypnozoites (i.e., primaquine or tafenoquine)

- If commercially available IV artesunate cannot be obtained within 24 hrs, CDC should be contacted and interim treatment with an effective oral antimalarial should be initiated. Discontinue oral therapy and give IV artesunate when available.
    - Interim oral treatment options:
        - Artemether-lumefantrine (preferred)
        - Atovaquone-proguanil
        - Quinine
        - Mefloquine
- Initiate IV artesunate with 2.4 mg/kg/dose at 0, 12, and 24 hrs. After the first 3 doses, assess a blood smear collected 4 hrs after the last dose of IV artesunate. Continue or change the treatment plan based on table 7 below.

  Table 7: Treatment plan after the initial course of IV artesunate

Parasite density ≤1% and patient able to tolerate oral therapy	Transition to full treatment course with oral regimen. Oral options: artemether-lumefantrine (preferred), atovaquone-proguanil, quinine + doxycycline or clindamycin, mefloquine (if no alternatives)
Parasite density ≤1% and patient unable to tolerate oral therapy	Continue artesunate 2.4 mg/kg/dose once daily for up to 6 additional days (maximum 7 days); transition to full treatment course with an oral regimen (options above) when able.
Parasite density >1%	Continue artesunate 2.4 mg/kg/dose once daily until parasitemia ≤1% (maximum of 7 days), then transition to full treatment course with an oral regimen (options above).

- Per expanded-use IND, IV artesunate could also be used in patients with confirmed malaria who cannot tolerate oral medications despite use of antiemetics

WHO guideline[9]:

- First-line treatment for severe malaria in adults and children (including infants, pregnant and lactating women)
    - Give artesunate IV or IM for at least 24 hrs and until patient able to tolerate oral medication
    - Transition to oral artemisinin-based combination therapy to complete treatment when able

Warnings, Precautions, and Adverse Effects[8,12,13]

- Contraindications
    - History of serious hypersensitivity reaction (i.e., anaphylaxis) to artesunate
- Warnings and Precautions
    - Hypersensitivity
        - Monitor for signs, including dyspnea, rash, and hypotension during administration; consider alternative therapy if reaction occurs.
    - Post-Treatment Hemolysis
        - Delayed hemolysis (≥7 days after start of therapy) has occurred and in some cases may require transfusion. Patients should be monitored for 4 weeks post-treatment for hemolytic anemia.
    - Embryo-Fetal Toxicity in Animals
        - Administration of IV artesunate early in gestation led to embryolethality in rats; this was also observed with oral administration in monkeys, rabbits, and rats.
        - Clinical relevance is uncertain as human experience with artesunate has not shown adverse fetal or maternal outcomes.

- Adverse Effects
    - Most common: acute renal failure (~9%), hemoglobinuria (~7%), jaundice (~2%), neurological side effects (balance impairment, confusion, tremor, weakness; ~1%)
    - Serious: delayed hemolysis/immune-mediated hemolytic anemia, hypersensitivity/anaphylaxis
- Pregnancy
    - IV artesunate is considered safe in pregnant women as no harmful effects have been observed in humans, though clinical data are limited for first trimester administration. Given the life-threatening nature of severe malaria to both pregnant women and their fetuses, treatment with IV artesunate outweighs possible risks. Guidelines recommend that treatment not be withheld in pregnancy.
- Breastfeeding
    - DHA is excreted in human breast milk in low amounts for up to 6 hrs post maternal dose at levels which are not expected to cause adverse events in the breastfeeding infant. Guidelines recommend treatment not be withheld in lactating women. The decision to breastfeed during therapy should be made weighing the infant's risk of exposure with the benefits of breastfeeding.

Interactions[12,13]

Table 8: Drug-drug interactions

Drugs	Interactions
Strong UGT inducers (i.e., carbamazepine, rifampin, phenytoin), ritonavir, neviripine	Concomitant use with artesunate may decrease exposure to DHA and lead to reduced efficacy
Strong UGT inhibitors (i.e., diclofenac, axitinib, imatinib, vandetanib)	Concomitant use with artesunate may increase exposure to DHA and lead to increased risk of adverse events

UGT: UDP-Glucuronosyltransferase

Dosage and Administration[8,9,12,13]

- Adult and pediatric patients: 2.4 mg/kg/dose given as slow IV bolus over 1-2 minutes at 0, 12, and 24 hrs
    - After initial 24 hrs, can be given once daily for up to 7 days total therapy based on parasitemia burden and ability to tolerate oral therapy (see Table 7 above)
    - Treatment should be followed by full course of appropriate oral antimalarial agent
    - In patients infected with *P. vivax* or *P. ovale*, artesunate should be administered with a concomitant agent active against liver hypnozoites
    - Alternative route of administration: IM injection into anterior thigh (not an FDA approved route)
- Dose modifications
    - Dosing is based on actual body weight (no adjustments for obesity)
    - No renal/hepatic dose adjustments required

Monitoring Parameters[8,13]

- Patients should be monitored for signs and symptoms of hypersensitivity to artesunate.
- Weekly lab monitoring should be performed in all patients treated with IV artesunate for 4 weeks post-treatment to evaluate for signs of hemolytic anemia. Labs should include:
    - Hemoglobin
    - Haptoglobin
    - Reticulocyte count
    - Lactate dehydrogenase (LDH)
    - Total bilirubin

How Supplied/Cost[12,13]

- Artesunate is supplied as a sterile white powder for reconstitution in 20 mL single-dose vials
    - 1 vial contains 110mg artesunate
    - 12 mL sterile phosphate buffer diluent supplied in single-dose vial
        - 11 mL required for reconstitution to concentration of 10mg/mL; resultant solution should be colorless
        - Must be administered within 1.5 hrs of reconstitution (discard excess)
- Artesunate is available for purchase from Cardinal in 220mg and 440mg quantities
    - 220mg cost: $9,960
    - 440mg cost: $19,920
- Cost estimation
    - For 70kg patient:
        - 2.4 mg/kg = 168mg (2 vials/dose)
        - 3 doses in 1st 24 hours = 6 vials

- Minimum cost per course = $29,880
- If therapy continued past first 3 doses, subsequent daily cost = $9,960/day
- If continued for maximum 7 days, cost = $89,640

Utilization
In 2018, 2 patients received IV artesunate at Nebraska Medicine (one pediatric, one adult). Estimated utilization <1 patient/month.

Pharmacoeconomic Analysis[18-20]
Pharmacoeconomic analyses (see table 9 below) have shown IV artesunate to be cost-effective and affordable compared to IV quinine when considering additional clinical benefit achieved with this therapy. This is no longer as relevant as IV quinine is no longer recommended as first-line therapy and is not marketed in the United States.

Table 9: Pharmacoeconomic analysis

	Lubell Y. et al, *Bull World Health Organ*. 2011	Lubell Y. et al, *Trop Med Int Health.* 2009
Type of analysis	Cost-effectiveness	Cost-effectiveness
Population	Most Adults	Children
Perspective	Provider (Asia)	Provider (Sub-Saharan Africa)
Model structure	Not reported	Decision tree
Currency	USD (2008)	USD (2009)
Time horizon	Immediate	Immediate
Comparators	Artesunate versus quinine	Artesunate versus quinine
Cost inputs	Drug cost; inpatient cost	Hotel cost; drug cost.
Outcomes	Cost per death averted increment with artesunate: USD 135.6	Cost per death averted increment with artesunate: USD 123 Cost per disability-adjusted life year (DALY) averted increment with artesunate: USD 3.8
Sensitivity analyses	Probabilistic sensitivity	One-way sensitivity; probabilistic sensitivity

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Appendix: Summary of Safety Issues and Implications for Pharmacy Operations

Characteristic	Summary
Medication Information	
Drug generic name (brand name)	Artesunate (Artesunate for Injection ™)
Drug manufacturer	Amivas, LLC
Schedule of medication	None
Anticipated use per month, anticipated patient population	<1 patient/month
Route of administration	Intravenous bolus
Preparation (for pharmacy personnel)	12 mL of sterile 0.3 M pH 8.0 sodium phosphate buffer sterile diluent is provided. Withdraw 11 mL of the diluent and inject into the artesunate vial to get a final concentration of 10 mg/mL. Gently swirl for up to 5-6 min until powder is fully dissolved. Do not shake. Final solution should be colorless with no particulate matter. Discard unused drug.
Is bedside dilution appropriate?	No ☒ Yes ☐
Stability	Dose must be administered within 1.5 hrs of reconstitution
Recommended storage conditions for medication, and how to manage excursions outside these conditions	Unused vials of artesunate and sterile diluent should be stored in carton at controlled room temperature (20-25ºC); excursions to 15-30ºC permitted. Avoid heat and light exposure. Freezing not permitted. Artesunate should not be used beyond expiration date.
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Operations Information	
Is filtration required during preparation or administration of the IV medication?	No ☒ Yes ☐ N/A ☐

*If **yes** for administration, ensure Willow adds filter information to admin instructions*	
Can medication doses be sent to patient care units via pneumatic tube system? See IC24. *If **no**, and not already addressed in IC24, add to policy IC24—contact Theresa Micheels.*	No ☒ Yes ☐ N/A ☐
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No ☒ Yes ☐
Safety/Policy Information	
Will this impact a dynamic alternative alert?	No ☒ Yes ☐
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Look-Alike-Sound-Alike (LASA)) list or confused names list? If not, is the medication expected to be added to the list? https://www.ismp.org/tools/tallmanletters.pdf http://www.ismp.org/Tools/confuseddrugnames.pdf	No ☒ Yes ☐
Does the product package insert currently have any boxed warnings? For what?	No ☒ Yes ☐
Is this medication a hazardous agent? *If **yes**, Med Safety to update policy MM10 Attachment A*	No ☒ Yes ☐
Is this medication classified as chemotherapy per AHFS 10:00? *If **yes**, Drug Policy to update policy MM11 Attachment A*	No ☒ Yes ☐
Is the medication a vesicant or irritant? *If **yes**, ensure Willow flags as vesicant or irritant on MAR.*	No ☒ Yes ☐
Is this a high-alert medication that requires an indication? See MM02. *If **yes**, Med Safety to update policy MM02*	No ☒ Yes ☐ Indication required for anti-infective; not high alert
Are there contraindications or significant warnings against medication use?	No ☐ Yes ☒ Contraindicated with allergy to artesunate
Is special administration or monitoring recommended when starting therapy with this medication (eg. Telemetry, BPetc)? *If **yes,** Med Safety to review at Medication Management Committee*	No ☒ Yes ☐
Is there unique dosing with administration (titration, guidance for determining dose, etc.)	No ☐ Yes ☒ Guidance for determining duration of use (see CDC guidelines)
Is this medication on the ISMP “Do Not Crush” list?	No ☒ Yes ☐
Does this medication require a Central Line for administration?	No ☒ Yes ☐
Is this medication infused via an infusion pump? *If **yes**, Med Safety to add to infusion pump library*	No ☒ Yes ☐
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No ☒ Yes ☐
Does the medication require precautions for disposal? What kind? See EC20 Disposal of Pharmaceutical Products; EC11 Chemo Drugs-Safety Precautions for Administration	No ☒ Yes ☐
Does this medication need to be considered for auto-wasting on the MAR or another avenue for documenting waste?	No ☒ Yes ☐

Will the medication be restricted: • To a specific level of care (LOC)? See TX 24: Admission, Transfer and Discharge for Defined Levels of Care. • To a specific location? • To specific services/ providers? • To providers credentialed in deep sedation or general anesthesia? • To patients who are on the medication prior to admit?	No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☐ Yes ☒ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐

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