Clinical Policy Title:	artesunate
Policy Number:	RxA.656
Drug(s) Applied:	artesunate
Original Policy Date:	09/14/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

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.

Limitation(s) 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
artesunate	severe malaria	2.4 mg/kg intravenously at 0 hours, 12 hours, and 24 hours and thereafter once daily until the patient is able to tolerate oral antimalarial therapy.	2.4 mg/kg

Dosage Forms

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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Severe malaria (must meet all):

1. Diagnosis of malaria confirmed by microscopy or members with strong clinical suspicion of malaria for whom a timely, reliable microscopic diagnosis is not available;
2. Member needs parenteral treatment due one or more of the following reasons (must meet a or b):

a. Severe malaria based on at least one of the following (i - x):
   i. High parasite density (≥5%)
   ii. Impaired consciousness
   iii. Seizures
   iv. Circulatory collapse/shock
   v. Pulmonary edema or acute respiratory distress syndrome (ARDS)
   vi. Acidosis
   vii. Acute kidney injury
   viii. Abnormal bleeding or disseminated intravascular coagulation (DIC)
   ix. Jaundice (must be accompanied by at least one other sign)
   x. Severe anemia (Hb <7 g/dL)

b. Member has inability to take oral medications despite attempt after an oral antiemetic;

3. If severe malaria is due to *P.vivax* or *P.ovale*, member is given concomitant therapy with an antimalarial agent such as an 8-aminoquinoline drug, according to the prescriber;
4. Dose does not exceed 2.4mg per kg;

Approval Duration
Commercial: 7 days (one-time authorization)
Medicaid: 7 days (one-time authorization)

II. Continued Therapy Approval

A. Severe malaria

1. Re-authorization is not allowed. Members must meet initial approval criteria. Review initial approval criteria for relapses or new cases of severe malaria.

Approval Duration
Commercial: Not applicable
Medicaid: Not applicable

III. APPENDICES

APPENDIX A: Abbreviation/Acronym Key
ARDS: Acute respiratory distress syndrome
DIC: Disseminated intravascular coagulation
CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug name	Dosing Regimen	Dose Limit/Maximum Dose
Coartem®	Coartem® tablets should be administered over 3-days for a total of 6 doses: an initial dose of 80 mg artemether/480 mg lumefantrine orally, second dose after 8 hours and then twice daily (morning and evening) for the following two days. • The adult dosage for patients with bodyweight of 35 kg and above is 4 tablets per dose for a total of 6 doses • The number of tablets per dose for children is	8 tablets/day (total of 6 doses over 3 days)

Drug name	Dosing Regimen	Dose Limit/Maximum Dose
	determined by bodyweight: ○ 5 to <15 kg – 1 tablet ○ 15 to <25 kg – 2 tablets ○ 25 to <35 kg – 3 tablets ○ 35 kg and over – 4 tablets	
atovaquone-proguanil (Malarone®)	Adults: 1000 mg atovaquone/400 mg proguanil hydrochloride orally once daily for 3 days. Pediatrics: Dosage based on body weight (see package insert).	See dosing regimen
quinine sulfate (Qualaquin®)	Adults (≥ 16 years of age): 648 mg (two capsules) every 8 hours for 7 days Patients with severe chronic renal impairment: one loading dose of 648 mg (two capsules) followed 12 hours later by 324 mg (one capsule) every 12 hours for 7 days.	1944 mg/day
mefloquine	For treatment of mild to moderate malaria in adults caused by P. vivax or mefloquine susceptible strains of P. falciparum: 1,250 mg orally as a single dose, or alternately, 750 mg orally as initial dose then 500 mg orally at 6 to 12 hours after initial dose. For patients with acute P.vivax malaria, 1250 mg orally as a single dose; subsequent treatment with an 8-aminoquinolone derivative agent (eg, primaquine) is suggested to avoid relapse after initial treatment of acute infection.	1250 mg/day
chloroquine	1,000 mg (600 mg base) orally, then 500 mg (300 mg base) orally in 6 to 8 hours, then 500 mg (300 mg base) orally once daily for 2 days.	1 g (600 mg base) orally as initial dose(s) for malaria treatment; otherwise, 500 mg/dose (300 mg base/dose) orally.
hydroxychloroquine (Plaquenil®)	800 mg (620 mg base) orally, then 400 mg (310 mg base) orally at 6, 24, and 48 hours after the initial dose for a total dose of 2 g (1.55 g base).	See dosing regimen
primaquine	52.6 mg (30 mg base) orally once daily for 14 days is recommended by guidelines. The FDA-approved dose for P. vivax infection is 26.3 mg (15 mg base) orally once daily for 14 days.	15 mg base orally daily; however higher doses of 30 mg base orally daily have been used.

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):

- Hypersensitivity (eg, anaphylaxis) to artesunate or any component of the formulation.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- According to CDC guidelines, intravenous artesunate is suggested as the drug of choice for the treatment of severe malaria, regardless of Plasmodium species; initiate treatment as soon as possible. Intravenous artesunate is available as part of an expanded-use investigational new drug protocol, and may be obtained through CDC by contacting the malaria hotline; while waiting for intravenous artesunate, consider interim treatment with an oral antimalarial agent. The preferred antimalarial for interim oral treatment is artemether-lumefantrine (Coartem®) because of its fast onset of action. Other oral options include atovaquone-proguanil (Malarone®), quinine, and mefloquine. Intravenous or oral clindamycin and tetracyclines, such as doxycycline, are not adequate for interim treatment. When intravenous artesunate arrives, immediately discontinue the oral medication and start parenteral treatment. Each dose of intravenous artesunate is 2.4 mg/kg. A dose of intravenous artesunate should be given at 0, 12, and 24 hours.

References

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	07/09/2020	09/14/2020
Policy was reviewed: 1. Statement about provider sample "The provision of provider samples does not guarantee coverage…" was added to clinical Policy. 2. Appendix A was updated to include abbreviations CDC and FDA. 3. Appendix B: Therapeutic alternative was updated to add verbiage "Below are	06/30/2021	09/14/2021

suggested therapeutic alternatives based on clinical guidance..". 4. Appendix B: Therapeutic Alternatives was updated to include maximum dose for Coartem, “8 tablets/day (total of 6 doses over 3 days)…” and dosing regimen for Coartem, “of 80 mg artemether/480 mg lumefantrine orally...”. 5. Appendix B: Therapeutic Alternatives was updated to include “1000 mg atovaquone/400 mg proguanil hydrochloride orally once daily for 3 days…”. 6. Appendix B: Therapeutic Alternatives maximum dose for quinine sulfate was updated to include “1944 mg/day.” 7. Appendix B: Therapeutic Alternatives was updated to include dosing regimen for mefloquine, “1,250 mg orally as a single dose, or alternately, 750 mg orally as initial dose then 500 mg orally at 6 to 12 hours after initial dose…” and its respective maximum dose “1250 mg/day.” 8. Appendix B: Therapeutic alternative was updated to include alternative drugs chloroquine, hydroxychloroquine, and primaquine; also updated to include their respective dosing regimens and maximum doses. 9. Appendix B: Therapeutic alternative was updated to remove “artemether-lumefantrine” from therapeutic alternative table as the drug is available by brand name “Coartem®” only.’ 10. Appendix B: Therapeutic alternative was updated to remove brand-name Lariam from therapeutic alternative table as its discontinued. 11. Statement about drug listing format in Appendix B is updated to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only." was updated. 12. References were reviewed and updated.		