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Policy Number: C8633-A

Antimalarial Agents

PRODUCTS AFFECTED

Arakoda (tafenoquine succinate), atovaquone-proguanil, chloroquine phosphate, Coartem (artemether-lumefantrine), Krintafel (tafenoquine), Malarone (atovaquone-proguanil), mefloquine, primaquine phosphate, Qualaquin (quinine sulfate), quinine sulfate

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Malaria prophylaxis or treatment

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PROPHYLAXIS OF PLASMODIUM FALCIPARUM MALARIA:
1. Documentation member is travelling to a destination at risk of malaria infection within the next 14

days [DOCUMENTATION REQUIRED OF DESTINATION AND TRAVEL DATES]
AND

2. Documentation of previous trial/failure or absolute contraindication to doxycycline OR member is travelling to an area with doxycycline resistant malaria per the CDC's Yellow Book (Health Information for International Travel 2024)
   MOLINA REVIEWER: Verify member's claims history. Members with chronic doxycycline use would not require additional prophylaxis meds unless traveling to an area of resistance. Avoid redirecting to doxycycline in pregnant members.
   AND
3. Documentation of previous trial/failure or absolute contraindication to chloroquine OR traveling to an area where chloroquine-resistant P. falciparum malaria is present, per the CDC's Yellow Book (Health Information for International Travel 2024)

B. TREATMENT OF UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA:

1. Documentation of diagnosis of active malaria infection and region where member acquired infection
   AND
2. Prescriber attestation that a report has been submitted to state health department (Malaria is a nationally notifiable disease, and all cases should be reported to the state health department)
   AND
3. For coverage of any product other than chloroquine, documentation of infection transmission from a chloroquine-resistant region.
   AND
4. For coverage of atovaquone-proguanil, documentation that member had transmission of infection in an area of unknown chloroquine resistance

CONTINUATION OF THERAPY:
NA

DURATION OF APPROVAL:
Initial authorization: 3 months or CDC recommended length of treatment, Continuation of therapy: NA

PRESCRIBER REQUIREMENTS:
None

AGE RESTRICTIONS:
Arakoda (tafenoquine): 18 years of age and older
Krintafel (tafenoquine): 16 years of age and older
All others: no limit

QUANTITY:
See Dosing limits by indication in the Appendix

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Antimalarials

FDA-APPROVED USES:
Arakoda (tafenoquine): indicated for the prophylaxis of malaria in patients aged 18 years and older

Chloroquine: indicated for Treatment of uncomplicated malaria due to susceptible strains of P. falciparum, P. malariae, P. ovale, and P. vivax., Prophylaxis of malaria in geographic areas where resistance to chloroquine is not present, and Treatment of extraintestinal amebiasis.
Chloroquine Phosphate Tablets do not prevent relapses in patients with vivax or ovale malaria because it is not effective against exoerythrocytic forms of the parasite. Limitations of use in Malaria: Do not use chloroquine phosphate tablets for the treatment of complicated malaria (high-grade parasitemia and/or complications e.g., cerebral malaria or acute renal failure). Do not use chloroquine phosphate tablets for malaria prophylaxis in areas where chloroquine resistance occurs, Resistance to Chloroquine phosphate tablets is widespread in P. falciparum, and is reported in P. vivax. Concomitant therapy with an 8-aminoquinoline drug is necessary for treatment of the hypnozoite liver stage forms of P. vivax and P. ovale.

Coartem (Artemether and lumefantrine): indicated for treatment of acute, uncomplicated malaria infections due to Plasmodium falciparum in patients 2 months of age and older with a bodyweight of 5 kg and above. Coartem tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported.
Limitations of use: Coartem tablets are not approved for patient with severe or complicated P. falciparum malaria. Coartem tablets are not approved for the prevention of malaria.

Krintafel (tafenoquine): indicated for the radical cure (prevention of relapse) of Plasmodium vivax malaria in patients aged 16 years and older who are receiving chloroquine therapy for acute P. vivax infection.
Limitations of Use: Krintafel is NOT indicated for the treatment of acute P. vivax malaria. The concomitant use of Krintafel with antimalarials other than chloroquine is not recommended because of the risk of recurrence of P. vivax malaria.

Malarone (atovaquone and proguanil): indicated for Prophylaxis of Plasmodium falciparum malaria, including areas where chloroquine resistance has been reported and treatment of acute, uncomplicated P. falciparum malaria. Note: CDC also recommends atovaquone/proguanil as prophylaxis for other Plasmodium species. CDC guidelines also recommend atovaquone/proguanil as an alternative agent for chloroquine- sensitive *Plasmodium* species, for chloroquine-resistant *Plasmodium vivax or Plasmodium ovale*, and as alternative oral treatment for severe malaria after completion of IV therapy or as interim therapy pending IV therapy (CDC Yellow Book 2020).

Mefloquine: indicated for the treatment of mild to moderate acute malaria caused by mefloquine-susceptible strains of *P. falciparum* (both chloroquine-susceptible and resistant strains) or by *Plasmodium vivax*. There are insufficient clinical data to document the effect of mefloquine in malaria caused by *P. ovale* or *P. malariae*. Also indicated for the prophylaxis of *P. falciparum* and *P. vivax* malaria infections, including prophylaxis of chloroquine-resistant strains of *P. falciparum.*
NOTE: Patients with acute P. vivax malaria, treated with mefloquine, are at high risk of relapse because mefloquine does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse, after initial treatment of the acute infection with mefloquine, patients should subsequently be treated with an 8- aminoquinoline derivative (e.g., primaquine).

Primaquine: indicated for the radical cure (prevention of relapse) of vivax malaria.

Qualaquin (quinine), quinine sulfate: indicated only for treatment of uncomplicated Plasmodium falciparum malaria. Quinine sulfate has been shown to be effective in geographical regions where resistance to chloroquine has been documented.
Limitations of use: Qualaquin is not approved for treatment of severe or complicated P. falciparum malaria, prevention of malaria, or the treatment or prevention of nocturnal leg cramps.

COMPENDIAL APPROVED OFF-LABELED USES:
NA

APPENDIX

APPENDIX:
CDC Malaria Treatment (United States) https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html
CDC Yellow Book 2024 Prevention Table 5-28 Malaria chemoprophylaxis: dosing information
Individual product FDA labeling

Drug	Treatment of Malaria	Prophylaxis of Malaria
Arakoda (tafenoquine)	N/A	Loading dose: 200 mg (2 x 100 mg) daily for 3 days prior to travel; 200 mg (2 x 100 mg) once weekly until 7 days after exiting area; limit 6 months
Chloroquine Phosphate Each 250mg tablet of chloroquine phosphate tablet contains the equivalent of 150mg of chloroquine base	Adults: 2.5g (1.5g base) over 3 days Pediatrics: 16.6 mg (10mg base)/kg/dose (max 1000 mg) x 1, then 8.3 mg (5 mg base)/kg/dose (max 500 mg) x 3 doses	Adults: 500 mg (300 mg base) weekly starting 2 weeks prior to travel and continuing 4-8 weeks after exiting area Pediatrics: 8.3 mg (5 mg base)/kg/dose (max 500mg) weekly 2 weeks prior to travel and continuing 4-8 weeks after exiting area
Coartem (Artemether-Lumefantrine)	Adults and Children ≥35 kg: 4 tablets/dose x 6 doses Pediatric (weight-based dosing): 25 to <35 kg: 3 tablets/dose x 6 doses 15 to <25 kg: 2 tablets/dose x 6 doses 5 to <15 kg: 1 tablet/dose x 6 doses	
Krintafel (tafenoquine)	300 mg (150 mg x 2 tablets) once	
Malarone (Atovaquone-Proguanil) Adult tablet contains 250 mg atovaquone and 100 mg proguanil. Pediatric tablet contains 62.5 mg atovaquone and 25 mg proguanil.	Adults and children >40 kg: 4 adult strength tablets daily for 3 days Pediatric (weight-based dosing) daily for 3 days 31 to 40 kg: 3 adult strength tablets 21 to 30 kg: 2 adult strength tablets 11 to 20 kg: one adult strength tablet 9 to 10 kg: 3 pediatric tablets 5 to 8 kg: 2 pediatric tablets	Adults and children >40 kg: 1 adult strength tablet once daily, 1-2 days before entering endemic area continuing to 7 days after exiting area. Pediatric (weight-based dosing): 1-2 days before entering endemic area continuing to 7 days after exiting area 31 to 40 kg: 3 pediatric strength tablets 21 to 30 kg: 2 pediatric strength tablets 11 to 20 kg: 1 pediatric tablet 8 to <10 kg: three-quarters pediatric tablet 5 to <8 kg: one-half pediatric tablet

Mefloquine	Adults: 1250 mg total single oral dose or divided into 2 doses Pediatrics: 25 mg/kg (max 1250mg) total divided into 2 doses	Adults and pediatrics >45 kg: 250 mg once weekly starting at least 2 weeks prior to travel and continuing 4 weeks after exiting area Pediatrics (weight-based dosing): starting at least 2 weeks prior to travel and continuing 4 weeks after exiting area 30 to 45 kg: three-quarters tablet (187.5 mg) 20 to 30 kg: one-half tablet (125 mg) >9-19 kg: one-quarter tablet (62.5 mg) 9kg or less: 5 mg/kg/dose
Qualaquin/ QuiNINE Sulfate	Ages ≥16 years: 648 or 650 mg every 8 hours for 7 days Ages ≥1 years: 10 mg/kg/dose (Max: 650mg/dose) every 8 hours for 3 day	

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Atovaquone-proguanil is administered daily with food beginning one to two days prior to exposure, during exposure, and for one week following exposure. Mefloquine is administered weekly beginning at least two weeks prior to exposure, during exposure, and for four weeks following exposure.
Doxycycline has activity against chloroquine-sensitive and chloroquine-resistant P. falciparum, as well as the other malaria species that cause human malaria. Comparative trials have demonstrated equivalent efficacy of doxycycline with mefloquine (e.g., 93 to 99 percent). Doxycycline can provide some protection against infection with some rickettsia infections (e.g., scrubtyphus) and Leptospira species. However, doxycycline does not prevent the development of residual hepatic hypnozoite forms of P. vivax or P. ovale malaria. Thus, for those with extended exposure to areas with high rates of infection due to these species, presumptive anti-relapse therapy with primaquine may be necessary to prevent relapse. Chloroquine is administered once weekly starting one week prior to exposure, once weekly while in the malaria endemic area, and then once weekly for four weeks following exposure. Primaquine is administered daily beginning one to two days prior to exposure, once daily during exposure, and daily for seven days following exposure.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Antimalarial agents are considered experimental/investigational and therefore, will follow Molina's Off-Label policy.
Contraindications to Arakoda (tafenoquine) include: G6PD deficiency or unknown G6PD status, Breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if G6PD status is unknown, Patients with a history of psychotic disorders or current psychotic symptoms, Known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of ARAKODA.
Contraindications to chloroquine include: Use of chloroquine phosphate tablets for indications other than acute malaria is contraindicated in the presence of retinal or visual field changes of any etiology, Use of chloroquine phosphate tablets is contraindicated in patients with known hypersensitivity to 4-aminoquinoline compounds.
Contraindications to Coartem (artemether and lumefantrine) include: Known hypersensitivity to artemether, lumefantrine, or to any of the excipients, Coadministration of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort with Coartem Tablets.
Contraindications to Malarone (atovaquone and proguanil hydrochloride), atovaquone and proguanil hydrochloride include: Known serious hypersensitivity reactions to atovaquone or proguanil hydrochloride or any component of the formulation, Prophylaxis of P. falciparum malaria in patients with severe renal

impairment (creatinine clearance < 30 mL/min).
Contraindications to mefloquine include: known hypersensitivity to mefloquine or related compounds (e.g., quinine and quinidine) or to any of the excipients contained in the formulation. Mefloquine should not be prescribed for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders, or with a history of convulsions.
Contraindications to Primaquine include: Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency, pregnancy, acutely ill patients suffering from systemic disease manifested by tendency to granulocytopenia, such as rheumatoid arthritis and lupus erythematosus, patients receiving concurrently other potentially hemolytic drugs or depressants of myeloid elements of the bone marrow, use of quinacrine because quinacrine hydrochloride appears to potentiate the toxicity of antimalarial compounds which are structurally related to primaquine.
Contraindications to Qualaquin (quinine), quinine sulfate include: patients with prolongation of QT interval, myasthenia gravis, known hypersensitivity to quinine, mefloquine, or quinidine, optic neuritis.

OTHER SPECIAL CONSIDERATIONS:
Doxycycline is contraindicated in pregnant women and in children <8 years of age.
Qualaquin (quinine) has a black box warning for hematologic reactions.
Mefloquine has a black box warning for neuropsychiatric adverse reactions.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Arakoda TABS 100MG
Atovaquone-Proguanil HCl TABS 250-100MG
Atovaquone-Proguanil HCl TABS 62.5-25MG
Chloroquine Phosphate TABS 250MG
Chloroquine Phosphate TABS 500MG
Coartem TABS 20-120MG
Krintafel TABS 150MG
Malarone TABS 250-100MG
Malarone TABS 62.5-25MG
Mefloquine HCl TABS 250MG
Primaquine Phosphate TABS 26.3 (15 Base)MG
Qualaquin CAPS 324MG
quiNINE Sulfate CAPS 324MG

REFERENCES

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Products affected Diagnosis Required Medical Information Duration of Approval FDA-Approved Uses Appendix Available Dosage Forms References	Q1 2024
REVISION- Notable revisions: Products Affected Required Medical Information FDA-Approved Uses Appendix Contraindications/Exclusions/Discontinuation Other Special Considerations References	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file