WHO recommendations are to treat uncomplicated malaria from all species with artemisinin-based combination therapy (such as Coartem™) based on safety and effectiveness of the drug, as well as to help streamline treatment recommendations for malaria. CDC and WHO treatment guidelines now concur with recommendations for Coartem™ as first line agent with known chloroquine resistance or species not identified. The CDC currently recommends chloroquine-containing regimens as first line therapy for chloroquine-susceptible species of malaria, which differs from WHO recommendations. We have elected to streamline institutional recommendations to be in line with WHO recommendations when there is discrepancy, given local drug availability and that Coartem™ clears parasitemia faster than chloroquine.

Definitions
Uncomplicated malaria:
Persons with a positive blood smear OR history of recent possible exposure and no other recognized pathology who do not meet severe criteria

Severe malaria:
Persons with a positive blood smear OR history of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria:
- Parasitemia of ≥5%
- Impaired consciousness/coma
- Severe normocytic anemia
- Renal failure
- Pulmonary edema
- Acute respiratory distress syndrome
- Circulatory shock
- Disseminated intravascular coagulation
- Spontaneous bleeding
- Acidosis
- Hemoglobinuria
- Jaundice
- Repeated generalized convulsions

Chloroquine sensitivity:
- *P. falciparum* acquired in Central America (west of the Panama Canal), Haiti, and Dominican Republic
- All *P. malariae*, *P. knowlesi*, and *P. ovale*
- All *P. vivax* EXCEPT infections acquired in Papua New Guinea or Indonesia

<table>
<thead>
<tr>
<th>Uncomplicated malaria</th>
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<tbody>
<tr>
<td><em>P. falciparum</em> or not identified</td>
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<tr>
<td><em>P. vivax</em> or <em>P. ovale</em> chloroquine sensitive</td>
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<thead>
<tr>
<th>Severe malaria</th>
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<tr>
<td>All species</td>
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Supply information
- Pharmacy steps to obtaining Artesunate

Footnotes & References
<table>
<thead>
<tr>
<th>Plasmodium Spp.</th>
<th>Treatment Regimen</th>
<th>Duration</th>
<th>Comments</th>
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</thead>
</table>
| Uncomplicated malaria with *P. falciparum* or species not identified | **Chloroquine resistant, unknown, or sensitive:**  
*Preferred*
Artemether 20 mg-lumefantrine 120 mg (Coartem™) = 1 tablet  
5 - <15 kg: 1 tablet/dose  
15 - <25 kg: 2 tablets/dose  
25 - <35 kg: 3 tablets/dose  
≥35 kg: 4 tablets/dose  
The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose PO BID for the following 2 days.  
| Coartem™: 3 days | WHO recommends treatment with artemisinin-based therapies (ACTs) for all *P. falciparum*  
If patient used Malarone™ as chemoprophylaxis then use another treatment option  
Please see CDC guidelines for treatment of pregnant women during the first trimester [CDC Malaria Treatment Table](https://www.cdc.gov/malaria/pdfs/clinicians/treatment-guidelines.pdf)  
Coartem™ and Malarone™ should be taken with food, and are OK to crush |
| Alternative | Atovaquone 62.5 mg-proguanil 25 mg (Malarone™) = 1 peds tablet  
5 - <8 kg: 2 peds tablets PO daily  
8 - <10 kg: 3 peds tablets PO daily  
| Malarone™: 3 days | |
| | Atovaquone 250 mg-proguanil 100 mg (Malarone™) = 1 adult tablet  
10 - <20 kg: 1 adult tablet PO daily  
20 - <30 kg: 2 adult tablets PO daily  
30 - <40 kg: 3 adult tablets PO daily  
≥40 kg: 4 adult tablets PO daily | |

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**CDC Malaria Treatment Table**

**Coartem™** and **Malarone™** should be taken with food, and are OK to crush.
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<tr>
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<tbody>
<tr>
<td>Uncomplicated malaria with chloroquine sensitive P. vivax or P. ovale</td>
<td><strong>Preferred</strong>&lt;br&gt;Artemether 20 mg-lumefantrine 120 mg (Coartem™) = 1 tablet&lt;br&gt;5 - &lt;15 kg: 1 tablet per dose&lt;br&gt;15 - &lt;25 kg: 2 tablets per dose&lt;br&gt;25 - &lt;35 kg: 3 tablets per dose&lt;br&gt;≥35 kg: 4 tablets per dose</td>
<td>Coartem™: 3 days</td>
<td>Please see CDC guidelines for management during Pregnancy <a href="https://www.cdc.gov/malaria/diagnosis_treatment/treatment/index.html">CDC Malaria Treatment Table</a>. Treatment of <em>P. vivax</em> or <em>P. ovale</em> requires addition of second agent to eliminate dormant hepatic hypnozoites. There may be a role for chloroquine prophylaxis for patients unable to take primaquine, consult with ID/CDC for further guidance.</td>
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<td></td>
<td><strong>AND</strong>&lt;br&gt;Primaquine (after confirmation that NOT G6PD deficient AND NOT pregnant)&lt;br&gt;Adults (≥18 years): 30 mg primaquine base PO daily&lt;br&gt;Children (&lt;18 years): 0.5 mg/kg primaquine base PO daily (max: 30 mg/dose)</td>
<td>Primaquine: 14 days</td>
<td>Coartem™ clears parasites more quickly than chloroquine. Regimens used for chloroquine-resistant species of malaria can also be substituted for chloroquine-sensitive species of malaria as needed based on drug availability.</td>
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<td></td>
<td><strong>Alternative for chloroquine sensitive organisms:</strong>&lt;br&gt;Chloroquine phosphate (Aralen™) – dose based on chloroquine base&lt;br&gt;Adults (≥18 years): 600 mg base PO immediately, followed by 300 mg base PO at 6, 24, and 48 hours (total dose: 1,500 mg base)&lt;br&gt;Children: 10 mg/kg base (max: 600 mg) PO immediately, followed by 5 mg/kg base (max: 300 mg) PO at 6, 24, and 48 hours (total dose: 25 mg/kg base)</td>
<td>Chloroquine: 48 hours</td>
<td>If chloroquine is being used, check EKG for QT interval prior to dosing, given risk for QT prolongation. Coartem™ and Malarone™ should be taken with food, and are OK to crush. Chloroquine comes as a liquid formation, but if this cannot be obtained, then crushing the tablet is acceptable. Chloroquine phosphate – 250 mg of chloroquine phosphate is equivalent to 150 mg of chloroquine base (600 mg chloroquine base = 1,000 mg salt; 300 mg chloroquine base = 500 mg salt).</td>
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<td><strong>AND</strong>&lt;br&gt;Primaquine (after confirmation that NOT G6PD deficient AND NOT pregnant)&lt;br&gt;Adults (≥18 years): 30 mg primaquine base PO daily&lt;br&gt;Children (&lt;18 years): 0.5 mg/kg primaquine base PO daily (max: 30 mg/dose)</td>
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| Uncomplicated malaria with chloroquine resistant *P. vivax* or *P. ovale* | **Preferred**  
Artemether 20 mg-lumefantrine 120 mg (Coartem™) = 1 tablet  
5 - <15 kg: 1 tablet per dose  
15 - <25 kg: 2 tablets per dose  
25 - <35 kg: 3 tablets per dose  
≥35 kg: 4 tablets per dose  
The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose PO BID for the following 2 days.  
**AND**  
Primaquine (after confirmation that NOT G6PD deficient AND NOT pregnant)  
Adults (≥18 years): 30 mg primaquine base PO daily  
Children (<18 years): 0.5 mg/kg primaquine base PO daily (max: 30 mg/dose)  | Coartem™: 3 days | Please see CDC guidelines for management during Pregnancy [CDC Malaria Treatment Table](#)  
Treatment of *P. vivax* or *P. ovale* requires addition of second agent to eliminate dormant hepatic hypnozoites  
There may be a role for chloroquine prophylaxis for patients unable to take primaquine, consult with ID/CDC for further guidance  
Coartem™ clears parasites more quickly than chloroquine  
Regimens used for chloroquine-resistant species of malaria can also be substituted for chloroquine-sensitive species of malaria as needed based on drug availability.  
Coartem™ and Malarone™ should be taken with food, and are OK to crush |
| | **Alternative for chloroquine-resistant organisms:**  
Atovaquone 62.5 mg-proguanil 25 mg (Malarone™) = 1 peds tablet  
5 - <8 kg: 2 peds tablets PO daily  
8 - <10 kg: 3 peds tablets PO daily  
Atovaquone 250 mg-proguanil 100 mg (Malarone™) = 1 adult tablet  
10 - <20 kg: 1 adult tablet PO daily  
20 - <30 kg: 2 adult tablets PO daily  
30 - <40 kg: 3 adult tablets PO daily  
≥40 kg: 4 adult tablets PO daily  
**AND**  
Primaquine (after confirmation that NOT G6PD deficient AND NOT pregnant)  
Adults (≥18 years): 30 mg primaquine base PO daily  
Children (<18 years): 0.5 mg/kg primaquine base PO daily (max: 30 mg/dose) | Malarone™: 3 days |  |
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<tr>
<th>Plasmodium Spp.</th>
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</tr>
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</table>
| Uncomplicated malaria with *P. malariae* or *P. knowlesi* | **Preferred**  
*Artemether 20 mg-lumefantrine 120 mg (Coartem™)* = 1 tablet  
5 - <15 kg: 1 tablet per dose  
15 - <25 kg: 2 tablets per dose  
25 - <35 kg: 3 tablets per dose  
≥35 kg: 4 tablets per dose  
The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose PO BID for the following 2 days. | Coartem™:  
3 days | These species have no known chloroquine resistance, but Coartem™ clears parasites more quickly than chloroquine |
| | **Alternative**  
*Chloroquine phosphate (Aralen™)* – dose based on chloroquine base  
Adults (≥18 years):  
600 mg base PO immediately, followed by 300 mg base PO at 6, 24, and 48 hours (total dose: 1,500 mg base)  
Children:  
10 mg/kg base (max: 600 mg) PO immediately, followed by 5 mg/kg base (max: 300 mg) PO at 6, 24, and 48 hours (total dose: 25 mg/kg base) | Chloroquine:  
48 hours | If chloroquine is being used, check EKG for QT interval prior to dosing, given risk for QT prolongation  
Coartem™ should be taken with food, and are OK to crush  
Chloroquine comes as a liquid formation, but if this cannot be obtained, then crushing the tablet is acceptable.  
Chloroquine phosphate – 250 mg of chloroquine phosphate is equivalent to 150 mg of chloroquine base (600 mg chloroquine base = 1,000 mg salt; 300 mg chloroquine base = 500 mg salt) |
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| Severe malaria (all spp) | **Artesunate** (IV) is the first line recommended agent, available only under an expanded access investigational new drug (IND) protocol (Call CDC and see notes below)  
Adults and children ≥20 kg:  
2.4 mg/kg/dose at 0, 12 hours, and 24 hours  
Children <20 kg:  
3 mg/kg/dose at 0, 12 hours, and 24 hours  
Recommended oral anti-malarial drug (Artemether-lumefantrine) immediately while awaiting delivery of IV Artesunate. If oral medications are not tolerated, consider administration via nasogastric tube or after an antiemetic  
*Once parasitemia <1%, follow IV artesunate with a full 3-day follow-on course of:  
**Artemether 20 mg-lumefantrine 120 mg** (Coartem™) = 1 tablet  
5 - <15 kg:  1 tablet per dose  
15 - <25 kg:  2 tablets per dose  
25 - <35 kg:  3 tablets per dose  
≥35 kg:  4 tablets per dose  
The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose PO BID for the following 2 days.  
**Alternative once parasitemia <1%, follow IV artesunate with a full 3-day follow-on course of:**  
**Atovaquone 250 mg-proguanil 100 mg** (Malarone™) = 1 adult tablet  
10 - <20 kg:  1 adult tablet PO daily  
20 - <30 kg:  2 adult tablets PO daily  
30 - <40 kg:  3 adult tablets PO daily  
≥40 kg:  4 adult tablets PO daily  
**Atovaquone 62.5 mg-proguanil 25 mg** (Malarone™) = 1 peds tablet  
5 - <8 kg:  2 peds tablets PO daily  
8 - <10 kg:  3 peds tablets PO daily  
*For patients with **P. vivax** and **P. ovale** please also provide  
**Primaquine** (after confirmation that NOT G6PD deficient AND NOT pregnant)  
**Adults (≥18 years):**  
30 mg primaquine base PO daily  
**Children (<18 years):**  
0.5 mg/kg primaquine base PO daily (max: 30 mg/dose)  
Maximum duration of IV artesunate: 7 days  
If there is persistent parasitemia at the end of the follow-on course, would warrant extension of Coartem until negative smears x2.  
If patient used Malarone™ as chemoprophylaxis then use another treatment option  
IV quinine is not available in the US.  
Delayed hemolysis can occur ~1 week after artesunate treatment in patients with hyperparsitemia. Recommend follow up weekly CBCs for 28 days after initiation of Artesunate. (See page 11 of IND document)  
Monitor carefully for hypoglycemia during the course of therapy  
Blood smears should be repeated every 12 to 24 hours, until at least 2 consecutive blood smears are negative. Also, blood smear should be repeated at the end of treatment. (See page 19 of IND document)  
Coartem™ and Malarone™ should be taken with food, and are OK to crush. |
Footnotes:

https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table_120419.pdf

CDC MALARIA HOTLINE: 770-488-7788 (M-F, 9am to 5pm), 770-488-7100 (after hours)

Notes about acquisition of Artesunate: drug can only be acquired after communication with CDC, and CDC will provide paperwork, including the appropriate consent forms which need to be completed before pharmacy can mix the drug.

Emergency Use IRB Application: The IRBMED chair-on-call should be paged first to notify them of the emergency use of artesunate (not an FDA approved medication in the United States), and to get the shipping information necessary for the CDC to ship the medication. The chair-on-call can be reached by calling the Michigan Medicine operator (734-936-4000) or through the paging website (search “IRBMED”). An emergency use IRB application will need to be completed within 5 days.

References:

Infectious Disease and Pharmacist Steps for obtaining Artesunate

I. ID Consult Team and/or Primary Team:
   1. Contact the CDC MALARIA HOTLINE: 770-488-7788 (M-F, 9am to 5pm), 770-488-7100 (after hours).
      - The CDC will need some information about the case
      - The CDC will also need a pharmacist contact name and phone number. Please page the Research Pharmacy on call pharmacist (pager 2944) and/or Amy Skyles, PharmD, pager 1812, phone: 734-936-7469.
   2. CDC will email several forms, and the ID consult team and/or primary team need to complete the following forms:
      - Patient consent form
      - FDA 1572 form
      - IND report form
   3. Send an email to UMHS expanded access group (UM-Expanded-Access-Request@med.umich.edu).
   4. All completed forms will need to be emailed to the expanded access group, and the CDC
   5. Place an artesunate order in Michart. Search for “Artesunate Expanded Access IND 76,725.” Call an ID pharmacist if assistance is needed (pager 35903)
   6. Ensure the protocol is followed, which includes monitoring for hemolysis for 4 weeks following artesunate administration. The CDC recommends monitoring hemoglobin, reticulocyte count, haptoglobin, lactate dehydrogenase and total bilirubin.

II. Research Pharmacy (on call if after business hours, pager 2944):
   1. The CDC will call you to coordinate product shipment. Detroit Airport (McNamara Terminal) has a CDC office and may have artesunate supply. If they don't have supply on hand, it will be shipped from the closest warehouse, which is located in Chicago. A CDC representative will board the next available commercial flight with artesunate supply.
   2. Call Metro Delivery to arrange courier pick up of drug at the airport (Phone: 734-973-0973)
   3. The CDC representative will provide a name and contact information of the person delivering artesunate to the courier. This information should be given to the courier. Additionally, the name of the courier service (likely Metro Courier), and the name and phone number of the driver should be given to the CDC representative. Coordinate a time of pick-up if possible.
   4. The courier should deliver the product to the Research Pharmacy when possible or to B2 or satellite pharmacy as appropriate after hours. Please communicate expected drop-off time and details with receiving pharmacy.
   5. Coordinate with preparing pharmacy and send satellite e-mail per standard practice.