INTRODUCTION TO THE CANADIAN MALARIA NETWORK

Parenteral ARTESUNATE and QUININE are available in Canada for the treatment of malaria. This package is provided with each request for intravenous ARTESUNATE or intravenous QUININE, and has been designed to assist you with patient care and use of these drugs.

If required, assistance is always available through Canadian Malaria Network (CMN) participants listed at www.travelhealth.gc.ca or www.phac-aspc.gc.ca/tmp-pmv/prof-eng.php.

Please note that these drugs are provided through the courtesy of Health Canada's Special Access Program, and therefore specific reporting is required when these agents are used.

REPORTING RESPONSIBILITIES

The dispenser (CMN depot site or satellite) is responsible for completing the Pharmacy Dispensing Record for Artesunate and Quinine (attached with package) each time a treatment course of IV artesunate or IV quinine is dispensed to (or on behalf of) a prescribing physician. This form must be filled out by the dispensing pharmacy and returned to the CMN within 24 hours following dispensing. The dispenser is responsible for ensuring that Form A and Form B are sent with every treatment course of drug.

The physician prescriber at the receiving institution is responsible for ensuring both Parenteral Therapy for Severe Malaria Form A (within 24 hours of starting treatment) and Form B (on day 7) are completed (attached with package, and available on the CMN website: http://www.phac-aspc.gc.ca/tmp-pmv/quinine/index-eng.php). In addition, any severe adverse events must be reported within 24 hours to the CMN using the Suspected Adverse Reaction Report Form (attached with package). The CMN will then submit, on behalf of the reporting physician, the Council for International Organizations of Medical Sciences Form I, as required by Health Canada's Special Access Program.

These forms document surveillance data, tolerance of antimalarial drug, and performance of the Canadian Malaria Network. If you have any concerns about the drugs received or questions about the CMN, reporting, or replenishing your stock, please contact us through the coordinating center e-mail at: CanadianMalariaNetwork@toh.on.ca

MALARIA DRUG REQUESTS:

To request a re-supply of either Artesunate or Quinine, please fill out the Canadian Malaria Network Drug Requisition form (attached with package) and send to: CanadianMalariaNetwork@toh.on.ca or fax to 613-739-6834.

Please fill in all spaces including the quantity of drugs used since your last shipment.

Revised: Dec 2016
ARTESUNATE
FOR THE TREATMENT OF SEVERE MALARIA

Artesunate is available in Canada through the Canadian Malaria Network**

Artesunate is recommended by the World Health Organization and the Committee to Advise on Tropical Medicine and Travel (CATMAT) as treatment of choice for severe and complicated malaria in both adults and children. IV artesunate has replaced IV quinine for most patients requiring parenteral therapy for the management of severe malaria.

*Note that due to the limited supply of artesunate, IV quinine is recommended for use (providing no contra-indications) in patients without severe malaria whose only indication for parenteral anti-malarial is vomiting or inability to tolerate oral therapy.*

NOTES ABOUT ARTE S UNATE:

- It is an artemisinin derivative currently used in many countries worldwide for the treatment of malaria.
- Advantages include: rapid activity, activity against all erythrocytic stages of the parasite, minimal resistance, very well tolerated, easy to administer, no dose adjustment for organ impairment and no significant drug interactions.
- In clinical studies, IV artesunate has shown either similar or improved efficacy over IV quinine for severe malaria. In addition, artesunate is associated with less adverse effects (e.g. hypoglycaemia) than IV quinine.
- Occasional side effects include anorexia, dizziness, light headedness, headache, taste alteration, nausea, diarrhea, reversible decrease in reticulocyte count, increased liver enzymes, bradycardia, rare allergic reactions (urticaria, pruritis, dyspnea). Recent reports of delayed haemolytic anemia have also been documented.
- Due to its short half-life (< 2 hours), malaria can recrudesce following the 3-day course of artesunate within days to weeks unless treatment is followed with a longer acting agent. Thus, follow-on therapy with a second agent is essential.
- A reminder that all patients requiring IV therapy (e.g. artesunate or quinine) for the treatment of malaria in Canada need to have —Parenteral Therapy for Severe Malaria—Forms A and B1 completed and returned to the Canadian Malaria Network. (Forms are provided with each supply of IV drug or available on the CMN website: http://www.phac-aspc.gc.ca/tmp-pmv/quinine/index-eng.php).
- Artesunate is not licensed in Canada, and is therefore considered an investigational drug.
- Artesunate has been made available in Canada through the Canadian Malaria Network (CMN) in collaboration with Health Canada’s Special Access Programme and the Public Health Agency of Canada. The artesunate supply used in Canada is obtained from either the Walter Reed Army Institute of Research (WRAIR) in the USA, or Guilin Pharmaceutical Co. Ltd in China. Note that the vial size, packaging and reconstitution directions differ between these supplies. Please follow the directions provided according to the supply you receive.
- The CMN National coordinating centre can be reached via email: CanadianMalariaNetwork@toh.on.ca

**The Canadian Malaria Network (CMN), in collaboration with Health Canada’s Special Access Program and the Public Health Agency of Canada, maintains supplies of intravenous artesunate and quinine at major medical centres across the country to facilitate rapid 24-hour access to effective treatment for severe malaria. More information or assistance in the management of malaria may be found in Chapter 7 of the 2014 Canadian Recommendations for the Prevention and Treatment of Malaria among International Travellers or by contacting the designated Canadian Malaria Network physician in your area. Both may be accessed through www.phac-aspc.gc.ca/tmp-pmv/prof-eng.php.
THERAPY FOR SEVERE *FALCIPARUM* MALARIA

## INTRA-VENOUS ARTESUNATE

**Generic Name:** Artesunate

**Classification:** Antimalarial; Anti-Protozoal agent; Artemisinin derivative

**Indications:** Treatment of choice for severe and complicated malaria and infections due to chloroquine-resistant or multi-drug resistant strains of malaria.

**Presentation:**

**US product (Walter Reed supply):** Artesunate 110 mg/vial; sterile powder with diluent (phosphate buffer) for reconstitution.

**Chinese product (Artesun®):** Artesunate 120 mg/vial; 1 x 2 mL amp sodium bicarbonate 50 mg/mL for reconstitution and 1 x 10 mL amp of 0.9% sodium chloride injection (normal saline or NS) per package.

**Storage:**

**US product (Walter Reed supply):** Store at 2-10 °C.

Buffer may be stored at 2-30 °C (note: phosphate crystals may form in the buffer at lower temperatures; these will dissolve if gently warmed). Discard if buffer is not clear and colourless upon rewarming.

**Chinese product (Artesun®):** Store below 30 °C. Protect from light.

**Reconstitution:**

**US product (Walter Reed supply):** Reconstitute each 110 mg vial of artesunate with 11 mL of phosphate buffer diluent. Gently swirl for 5 to 6 minutes for a resultant concentration of 10 mg/mL. May be mixed with 5 mL of 5% dextrose or NS prior to injection if desired.

**Chinese product (Artesun®):** Reconstitute each 120 mg vial of artesunate with the contents (2 mL) of the provided ampoule of sodium bicarbonate solvent Shake the vial (not too vigorously) for several minutes until the powder is completely dissolved and the solution is clear. (The solution should clear in a few minutes after reconstitution.) Discard if the solution does not clear or a precipitate is present.

For IV administration: Add the contents (10 mL) of the supplied ampoule of NS diluent to the vial containing the reconstituted artesunate solution. Shake to mix well. Solution should be clear. Discard if the solution appears cloudy or a precipitate is present. This will yield a concentration of artesunate of 10 mg/mL.

For IM administration (only if IV access cannot be obtained): add 4 mL of the supplied NS diluent to the vial containing the reconstituted artesunate solution. Shake to mix well. Solution should be clear. Discard if the solution appears cloudy or a precipitate is present. This will yield a concentration of artesunate of 20 mg/mL.

**Stability:** Stable 1 hour after reconstitution. Discard any unused solution. Drug should be administered as soon as possible following reconstitution or further dilution.

**Compatible Fluids:** Dextrose 5% in Water, Normal Saline

**Incompatible Fluids:** Water for injection (no data).

Revised: Dec 2016
**DOSAGE/ADMINISTRATION FOR SEVERE *FALCIPARUM* MALARIA:**

Currently, a 4-dose regimen of intravenous artesunate is recommended:
- For adults and children weighing 20 kg and over: 2.4 mg/kg IV at 0, 12, 24 and 48 hours. (Total dose is 9.6 mg/kg). Obese patients should be dosed based on actual body weight (i.e. no maximum dose).
- For children weighing less than 20 kg: 3 mg/kg IV at 0, 12, 24 and 48 hours. (Total dose is 12 mg/kg).

First dose should be administered STAT.
- Each dose should be administered IV push over 1 to 2 minutes following reconstitution of drug into an established IV line.
- The patient may be switched to oral therapy after a minimum of 24 hours (3 doses) of IV artesunate if they are able to tolerate oral medication at that time.

For IM administration (Chinese product): Preferred site of injection is anterior thigh; depending on the volume to administer, may need to divide dose and inject in several sites.

**ADDITIONAL INFORMATION:**
- Patient should be observed for 30 minutes following administration for signs of an allergic reaction (e.g. itching, swelling, shortness of breath, chest pain, watery eyes).
- Due to reports of delayed hemolytic anemia, patients require weekly CBCs for one month following treatment with artesunate.
- Dose adjustment of artesunate is not required in renal or liver dysfunction.
- **Pregnancy:** IV artesunate is preferred over IV quinine in the second and third trimesters. IV quinine is the preferred drug in women in the first trimester. If IV quinine is not readily available or is contraindicated, the benefit of artesunate in the first trimester outweighs the risk of inadequate treatment of severe malaria in both mother and fetus.
- Patients who meet criteria for severe malaria should receive a minimum of 24 hours (i.e., 3 doses) of parenteral artesunate before switching to oral follow-on therapy (irrespective of the patient’s ability to tolerate oral medication earlier)
- Due to its short half-life (< 2 hours), malaria can recrudesce following treatment with artesunate within days to weeks unless treatment is followed with a longer acting agent. Thus, follow-on therapy with a second agent is essential, and should be started 4 hours after the last IV artesunate dose.
- Although not routinely recommended, in emergency situations artesunate may be administered intramuscularly into the anterior thigh (e.g., in the rare event that venous access is not immediately possible.) Reconstitution instructions for the Chinese product for IM administration are provided above. For the US product (Walter Reed supply), the same preparation, dilution and dosage as for IV administration should be used.
- Unused stock must be returned to the pharmacy/distribution site.

**SECOND AGENT:**

Although rapid acting, artesunate does not completely eliminate all parasites. As a result, a second oral agent is required as follow-on therapy. The oral agent is started 4 hours after the last dose of IV artesunate. Malarone® is the preferred agent (unless patient had received prophylaxis with Malarone®, or CrCl <30 ml/min); quinine with either with doxycycline or clindamycin are alternatives.

If, in the rare case, patients cannot tolerate oral medication following the 4 doses of artesunate, options...
include continuing artesunate IV daily for up to 7 days total, or switching to a 7 day course of IV
doxycycline (100 mg Q12H or 2 mg/kg Q12H (max 100 mg) for pediatric (≥ 8 years old) patients; Special
Access drug) or IV clindamycin (10 mg/kg loading dose, followed by approximately 5 mg/kg IV Q8H).
Choice should be made in consultation with an Infectious Diseases specialist.

**ORAL FOLLOW-ON THERAPY:**
Start either a 3-day course of Malarone® tablets* (preferred) or a 7-day course of quinine with either
doxycycline or clindamycin.

The recommended doses of oral agents are listed in the following table:

<table>
<thead>
<tr>
<th>Oral Antimalarial Agents: Recommended Drug Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
</tr>
</tbody>
</table>
| Malarone® (Atovaquone/Proguanil)              | 4 adult tablets (taken all at once with food) daily for 3 days | According to weight:  
| Adult tablet: Atovaquone 250 mg/Proguanil 100 mg per tablet |                                       | 5-8 kg: 2 pediatric tablets daily x 3 days  
| Pediatric tablet: Atovaquone 62.5 mg/Proguanil 25 mg per tab |                                       | 9-10 kg: 3 pediatric tablets daily x 3 days  
| Quinine sulphate (Note: quinine sulphate 600 mg = 500 mg quinine base) | 600 mg orally Q8H for 7 days | 11 – 20 kg: 1 adult tablet daily x 3 days  
| Doxycycline (Note: Contraindicated if age < 8 years, during pregnancy or breastfeeding) | 100 mg BID for 7 days | 21 – 30 kg: 2 adult tablets daily x 3 days  
| Clindamycin (Note: use only if unable to take Malarone® or doxycycline) | 20 mg/kg/day orally, divided into 3 or 4 doses, for 7 days | 31 – 40 kg: 3 adult tablets daily x 3 days  
|                                                |                                                     | > 40 kg: 4 adult tablets daily x 3 days               |

*Note: quinine sulphate 600 mg = 500 mg quinine base*
ARTESUNATE ADVERSE EFFECTS:

Artesunate is very well tolerated in adults and children. Occasional side effects include anorexia, dizziness, light headedness, taste alteration, nausea, diarrhea, reversible decrease in reticulocyte count, increased liver enzymes, bradycardia, heart block, and rare allergic reactions (e.g. urticaria, pruritis, dyspnea).

**Hemolytic anemia:** Cases of delayed hemolytic anemia (either recurrent or persistent) following use of artesunate (8 to 32 days after therapy) for severe malaria have been reported worldwide. Patients with high pre-treatment parasitaemia may be at a higher risk. Although possibly attributable to the disease itself, there have been cases reported with the drug distributed through the CMN. Due to this risk, Health Canada and the CMN recommend a CBC be performed weekly for 4 weeks following treatment with parenteral artesunate to monitor patients for anemia. In addition, patients treated with IV artesunate should be counselled to report signs of hemolysis, such as dark urine, yellowing of skin or whites of eyes, fever, abdominal pain, pallor, fatigue, shortness of breath and/or chest pain.
THERAPY FOR SEVERE *FALCIPARUM* MALARIA

**QUININE DIHYDROCHLORIDE**

**Trade Name / Generic Name:** Quininject / Quinine dihydrochloride

**Classification:** Antimalarial; Anti-Protozoal agent; Antipyretic

**Indications:** Treatment of severe and complicated malaria and infections due to chloroquine-resistant or multi-drug resistant strains of malaria.

**Presentation:** Quinine dihydrochloride 600 mg/2 mL amp.

**Storage:** Store below 25°C. Protect from light.

**Reconstitution:** Not required.

**Stability:** Discard any unused solution.

**Compatible Fluids:** Normal Saline; Dextrose 5% in Water

**Incompatible Fluids:** None known.

**DOSAGE/ADMINISTRATION FOR SEVERE *FALCIPARUM* MALARIA:**

**LOADING DOSE:**
*Requires administration via IV pump:*
- Quinine dihydrochloride 7 mg/kg OR quinine base 5.8 mg/kg
- Diluted in 100 mL of isotonic fluid (D5W preferred) by intravenous infusion over 30 minutes, then start maintenance dose.
- Commence maintenance dose immediately after loading dose.

**EXCEPTIONS FOR LOADING DOSE:**
- Loading dose should **NOT** routinely be administered if patient has received quinine or quinIDine or a dose of mefloquine within the preceding 24 hours due to the risk of cumulative toxicity
  - Maintenance dosing should be used for these patients.
  - If history is unclear, and/or if benefits of a loading dose are felt to outweigh the risk, cardiac monitoring is recommended.
- A loading dose is **NOT** required if IV quinine is used in patients without severe malaria whose only indication for parenteral anti-malarial is vomiting or inability to tolerate oral therapy.

**MAINTENANCE DOSE:**
- Quinine dihydrochloride 10 mg/kg OR quinine base 8.3 mg/kg
- Diluted in 10 mL/kg of isotonic fluid (D5W preferred) by intravenous infusion over at least 2 hours.
• Repeat every 8 hours until indication (e.g., % parasitemia, minimum of 24 hours of therapy if severe malaria) for IV quinine therapy no longer exists and/or patient can swallow, then switch to oral therapy to complete treatment course (see below).
• If patient requires more than 48 hours of parenteral therapy, reduce the quinine maintenance dose to 5-7 mg/kg (dihydrochloride salt) every 8 hours to avoid accumulation.

**ADDITIONAL INFORMATION:**

• Intravenously, the drug should be given slowly (maximum rate 5 mg/kg salt per hour; exception: 7 mg/kg loading dose above) to avoid the risk of cardiovascular toxicity; pulse and blood pressure should be closely monitored and the rate of infusion attenuated if dysrhythmias occur.
• Due to the limited supply of IV artesunate, IV quinine is recommended for use (providing no contra-indications) in patients without severe malaria whose only indication for parenteral anti-malarial is vomiting or inability to tolerate oral therapy.
• Replace with oral therapy as soon as possible (see exception below). If IV quinine is prescribed for a patient who meets criteria for severe malaria, a minimum of 24 hours of parenteral therapy (i.e., 3 maintenance doses) should be administered before switching to oral therapy (irrespective of their ability to tolerate oral medication earlier)
• Therapy should be withdrawn immediately if signs of haemolysis appear.
• There are a number of side effects linked to quinine administration, known as cinchonism. Hypersensitive patients may react in this way even to small doses.
• Intramuscular administration should be used only as a last resort, since it is highly irritating and may cause focal necrosis and abscess formation.
• Parenteral quinIDine should be used only if parenteral quinine is unavailable; cardiac monitoring is required.

**QUININE ADVERSE EFFECTS:**

Cinchoinism (tinnitus, impaired hearing, headache, nausea, disturbed vision, vomiting, abdominal pain, diarrhea, vertigo), hypersensitivity (urticaria, pruritus, skin flushing, thrombocytopenia), fever, rashes, dyspnea, angioedema, precipitation of asthma, haemoglobinuria, hypoglycaemia (quinine-induced hyperinsulinaemia), hypoprothrombinaemia, renal failure, cardiotoxicity (dysrhythmias, asystole, hypotension, anginal symptoms), CNS disturbances, oculotoxicity (sudden blindness), injection site (abscess, focal necrosis and pain after IM administration).

**PRECAUTIONS:**

• Check for hypersensitivity to quinine or quinIDine before administration.
• Use with caution in patients with a history of cardiovascular disease, renal dysfunction, glucose-6-phosphate dehydrogenase deficiency, asthma or atopy, or myasthenia gravis.
• Monitor vital signs, blood glucose, and ECG if history of underlying cardiac disease.
• Avoid rapid injection.
• In seriously ill patients with renal failure, maintain the full dosage regimen for at least 48 hours.

**SECOND AGENT:**

A second agent (doxycycline or clindamycin) should be started either concurrently with IV quinine or as soon as possible after IV quinine. The second agent can usually be started when the patient can take oral therapy. If this is not possible, IV doxycycline (100 mg Q12H or 2 mg/kg Q12H (max 100 mg) for pediatric (≥ 8 years old) patients; Special Access drug) or IV clindamycin (10 mg/kg loading dose, followed by approximately 5 mg/kg IV Q8H) may be prescribed.
STEPDOWN THERAPY:
Stepdown to oral therapy as soon as possible with either a 3 day course of Malarone® tablets* (preferred, unless patient had received prophylaxis with Malarone®, or CrCl <30 ml/min) or oral quinine with either doxycycline or clindamycin to complete 7 day course.

The recommended doses of oral agents are listed in the following table:

### Oral Antimalarial Agents: Recommended Drug Doses

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ADULT DOSE</th>
<th>PEDIATRIC DOSE</th>
</tr>
</thead>
</table>
| **Malarone®** *(Atovaquone/Proguanil)* | 4 adult tablets (taken all at once with food) daily for 3 days | According to weight:  
5-8 kg: 2 pediatric tablets daily x 3 days  
9-10 kg: 3 pediatric tablets daily x 3 days  
11 – 20 kg: 1 adult tablet daily x 3 days  
21 – 30 kg: 2 adult tablets daily x 3 days  
31 – 40 kg: 3 adult tablets daily x 3 days  
> 40 kg: 4 adult tablets daily x 3 days |
| **Adult tablet:** Atovaquone 250 mg/Proguanil 100 mg per tablet | 600 mg orally Q8H for 7 days | 9 mg/kg orally Q8H for 7 days (max 600 mg/dose) |
| **Pediatric tablet:** Atovaquone 62.5 mg/Proguanil 25 mg per tab | 2 mg/kg BID for 7 days | 2 mg/kg (to a maximum of 100 mg) BID for 7 days |
| **Quinine sulphate** *(Note: quinine sulphate 600 mg = 500 mg quinine base)* | 100 mg BID for 7 days | 20 mg/kg/day orally, divided into 3 or 4 doses, for 7 days |
| **Doxycycline** *(Note: Contraindicated if age < 8 years, during pregnancy or breastfeeding)* | 20 mg/kg/day orally, divided into 3 doses, for 7 days | 20 mg/kg/day orally, divided into 3 doses, for 7 days |
| **Clindamycin** *(Note: use only if unable to take Malarone® or doxycycline)* | 2 mg/kg BID for 7 days | 2 mg/kg (to a maximum of 100 mg) BID for 7 days |
GUIDELINES FOR THE TREATMENT OF MALARIA

The following guidelines have been adapted from the 2013 Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers. Canada Communicable Disease Report, 2013; in press. Available at: http://www.phac-aspc.gc.ca/tmp-pmv/prof-eng.php

GENERAL PRINCIPLES OF MANAGEMENT

There are three main questions that must be addressed before initiating treatment.

1. **Is this infection** caused by *Plasmodium falciparum*? This is critical as astreatment varies according to the species of malaria.
2. **Is this a severe or complicated infection?** This can be determined using the table below. Severe or complicated malaria requires parenteral therapy and sometimes an exchange transfusion in those with 10% or greater parasitemia.
3. **Has the infection been acquired in an area of known drug-resistant malaria?** In most areas in the world where *falciparum* malaria is transmitted, it is caused by chloroquine resistant parasites. **When in doubt, treat all *falciparum* malaria as drug resistant.** For more information on malaria risk by geographic area, please refer to the Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers 2013 (http://www.phac-aspc.gc.ca/tmp-pmv/prof-eng.php).

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Laboratory test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostration/impaired consciousness</td>
<td>Severe anemia [haematocrit &lt; 20%; Hb &lt; 70 g/L (adults); &lt; 15%, &lt; 50 g/L (children)]</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Hypoglycemia (blood glucose &lt; 2.2 mmol/L)</td>
</tr>
<tr>
<td>Multiple convulsions</td>
<td>Acidosis (arterial pH &lt; 7.25 or bicarbonate &lt; 15 mmol/L)</td>
</tr>
<tr>
<td>Circulatory collapse/shock</td>
<td>ARF/Renal impairment (creatinine &gt; 265 umol/L)</td>
</tr>
<tr>
<td>Pulmonary edema (radiological)/ARDS</td>
<td>Hyperlactataemia (&gt; 5 mmol/L)</td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>Hyperparasitaemia#</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Haemoglobinuria (macroscopic)</td>
</tr>
</tbody>
</table>

ARDS: acute respiratory distress syndrome; ARF: acute renal failure

# Hyperparasitaemia is defined as:
- ≥2% in children <5 years
- ≥5% for non-immune* adults and children ≥5 years
- ≥10% for semi-immune** adults and children ≥5 yrs

*Non-immune = those born in non-endemic countries or low-transmission settings, such as travelers.
**Semi-immune = individuals with recent long-term residence in an endemic country and prior episodes of malaria. Note: Immunity is considered lost after a period of ≥ 6-12 months living outside of the malaria endemic country.


MANAGEMENT OF *FALCIPARUM* MALARIA

A detailed geographic history is essential to the management of malaria. *P. falciparum* malaria acquired in areas where drug resistance is known to occur should be treated as chloroquine-resistant.
Severe *P. falciparum* infections may have a mortality of ≥ 20%. These patients require immediate hospitalization and urgent intensive medical management. As a general rule, all non-immune patients with *P. falciparum* malaria, whether severe or not, should be considered for admission to hospital in order to ensure tolerance of antimalarials and to detect complications and early treatment failure.

All patients with severe *P. falciparum* infections, and all patients unable to tolerate oral drugs, should receive intravenous artesunate or quinine. In the treatment of severe malaria, parenteral artesunate is preferred over parenteral quinine, as it provides better outcomes, is better tolerated, and is easier to administer compared with IV quinine. *Due to the limited supply of IV artesunate, IV quinine is recommended for use (providing no contra-indications) in patients without severe malaria whose only indication for parenteral anti-malarial is vomiting or inability to tolerate oral therapy.*

Note that parenteral quinIDine is not recommended due to its cardiotoxicity and need for electrocardiographic monitoring.

Although artesunate and quinine are rapid acting, they do not completely eliminate all parasites. As a result, it is essential to prescribe a second agent, usually administered orally, as follow-on therapy. Atovaquone/proguanil (Malarone®) is usually the preferred agent; quinine with either doxycycline or clindamycin are alternatives. For assistance with treatment of severe malaria, please consult Chapter 7 of the 2013 Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers or the Canadian Malaria Network. Both may be accessed through www.phac-aspc.gc.ca/tmp-pmv/prof-eng.php.

Five percent or more of patients treated for malaria may fail treatment. Most patients fail within 1 month of treatment. To ensure patients are cured, it is important to repeat malaria thick and thin smears until negative for asexual forms and on day 7, and if there is any recurrence of symptoms.
TREATMENT OF MALARIA IN PREGNANCY

Pregnant women with malaria are more likely to develop severe disease compared to non-pregnant women. Malaria can result in significant morbidity and mortality in both pregnant woman and the fetus, including miscarriage, premature labour, low birth weight, and potentially death. Thus, it is essential that malaria in the pregnant patient be treated immediately, and the benefits of drug therapy outweigh any risks for both the mother and baby. Because pregnant women are more prone to hypoglycaemia, both from the infection and use of IV quinine, close monitoring of blood glucose is essential.

The following is a summary of the preferred drug regimens for treatment of malaria in pregnancy.

1. Uncomplicated, confirmed P. vivax or P. ovale or P. malariae malaria:
   - Chloroquine (same treatment schedule as with non-pregnant adults)

   **Note:** Primaquine phosphate should not be prescribed during pregnancy for radical cure of P. vivax or P. ovale infections. Following treatment with chloroquine, these patients should be maintained on chloroquine prophylaxis (500 mg salt or 310mg base orally once weekly) during their pregnancy and primaquine therapy prescribed after delivery if no contraindication.

2. Uncomplicated malaria caused by P. falciparum infection:
   - Oral quinine with clindamycin X 7 days

3. Complicated or severe malaria caused by P. falciparum:
   a) First trimester:
      - IV quinine (stepdown to oral after 24 hours when able) with addition of clindamycin (IV or oral—may be started 24 to 48 hours after initiation of IV quinine) X 7 days
   b) Second or third trimester:
      - IV artemunate, followed by a 7-day course of clindamycin

**Full doses of all antimalarials should be used in pregnant patients.**

**Note:** Atovaquone/proguanil (Malarone®) is generally not indicated for use in pregnant women due to a lack of adequate, well-controlled studies in pregnant women. However, use of Malarone® may be considered if the recommended treatment options are not tolerated, following assessment of the potential risks and benefits.

**REFERENCES:**

3. Treatment of Malaria (Guidelines for Clinicians). Centers for Disease Control and Prevention. Available at: [http://www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm](http://www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm)
REFERENCES:


Written communication, Intravenous Artesunate Integrated Product Team Walter Reed Army Institute of Research, Peter J. Weina, March 5, 2009.


ARTESUNATE EXPIRY DATE

CANADIAN MALARIA NETWORK (CMN)

Please note that the vials of parenteral Artesunate supplied by the Walter Reed Army Institute of Research (WRAIR) in the USA do not have an expiry date, only a manufacturing date.

The supplier (The United States Army Medical material Development Activity – USAMMDA, Fort Detrick Maryland) will inform the keeper of the medication (The Ottawa Hospital- Pharmacy Department) when the product can no longer be used.

Determination of the product expiry date is based on purity and potency tests performed on the malaria medication at regular intervals (q 12 months). This is in accordance with the FDA’s recommendations on stability testing of New Drug Substance Products.

Once The Ottawa Hospital has been informed of the upcoming expiry date, all centres and sites across Canada will be contacted and new supplies will be shipped to the corresponding destinations.

For any questions or concerns, please contact CanadianMalariaNetwork@toh.on.ca
CANADIAN MALARIA NETWORK
DRUG REQUISITION FORM

To: The Ottawa Hospital – General Campus

Attention: Pharmacy Research Technicians

Site Name: __________________________

PO Number: __________________________

Requested by: ________________________

Address: ____________________________

Telephone Number: ___________________

Date of Request: _____________________

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Quantity on Hand</th>
<th>Quantity Requested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artesunate 110 mg vials (US Product)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphate Buffer 12 ml vials (if USA supply)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artesunate 120 mg vials (Chinese Product)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine Dihydrochloride 600 mg/ 2 mL ampoules</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please complete the following table:

<table>
<thead>
<tr>
<th>DISPENSING(S) SINCE YOUR LAST SHIPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Name</td>
</tr>
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</tbody>
</table>

Please fax to 613-739-6834 or email to CanadianMalariaNetwork@toh.ca

Form Version: March 2017
PHARMACY DISPENSING RECORD FOR IV ARTESUNATE AND IV QUININE

REQUESTING AND/ OR ATTENDING PHYSICIAN [PHYSICIAN INFORMATION ONLY]

Name: ___________________________ Title: ___________________________
Hospital: ___________________________ Department: ___________________________
City: ___________________________ Province: ___________________________
Telephone: ___________________________ Email: ___________________________

PATIENT INFORMATION:

Initials (first/middle/last): ___________________________
Date of Birth (dd/mm/yy): ___________________________
Sex: □Male □Female
Weight: ____________ kg

PHARMACY DISPENSING SITE

City: ___________________________
Hospital: ___________________________

Prescribing Physician and/or Contact have consulted with an Infectious Disease Physician:
□Yes □No □Don't know

If no/don’t know, please remind the physician / requestor of the availability of the Canadian Malaria Network 24-hour Infectious Disease Contacts and information resources available on the CMN website (http://www.phac-aspc.gc.ca/tmp-pmv/quinine/)

Medication Dispensed (Including Information Package With Forms A And B)

□Artesunate + Phosphate buffer diluent (US Product)
  # Vials Artesunate: ____________
  # Vials Diluent: ____________

□Artesunate w bicarb prepackaged (Aretsun®) (Chinese Product)
  # Vials Artesunate: ____________
  # Vials Diluent: ____________

□Quinine (one kit of 7 ampoules)# Ampoules: ____________

Method of Shipping/Arrangements for Pick-Up and Delivery (Note: Artesunate (USA/WRAIR supply) must be shipped as a refrigerated item): ________________________________________________________________

______________________________________________________________

Date Dispensing Completed (dd/mm/yy) ___________________________ Time: ___________________________
Dispensed by (Name of Pharmacy Personnel): ___________________________ Phone Number: ___________________________

Complete and Return to the CMN Coordinating Centre within 24 Hours of Dispensing by E-Mail: CanadianMalariaNetwork@toh.on.ca or by Fax: 613-737-8164

Version: March 2017
**PARENTERAL THERAPY FOR SEVERE MALARIA - FORM A**

To be completed by the Attending Physician

| CMNID: |

---

1. Date of request (D/M/Y): ______/_____/_____

2. Drug requested (check all that apply):
   - [ ] US Artesunate* (US Product) LOT# ____________________________
   - [ ] Chinese Artesunate* (Chinese Product) LOT# ____________________________
   - [ ] Quinine LOT# ____________________________

   *For artesunate request, monitor CBC weekly for four weeks. Low risk for delayed hemolysis; if this occurs, the CMN must be notified.

3. REQUESTING/ATTENDING PHYSICIAN
   
   Name: ____________________________
   
   Hospital/site: ____________________________
   
   City: ____________________________ Province: ____________________________
   
   Tel#: ____________________________ Fax#: ____________________________
   
   Email: ____________________________

4. PATIENT DEMOGRAPHICS
   
   Initials (first/middle/last): ______/_____/_____
   
   Date of birth (D/M/Y): ______/_____/_____
   
   Sex: [ ] Male  [ ] Female  Pregnant: [ ] Yes  [ ] No
   
   Birth Country: ____________________________
   
   If <18 years, country of parental origin: ____________________________
   
   Canadian Resident?: [ ] Yes  [ ] No
   
   Visitor?: [ ] Yes  [ ] No

5. PATIENT TRAVEL INFORMATION
   
   Presumed country(ies) of acquisition:
   1) ____________________________  2) ____________________________  3) ____________________________
   
   Date departed Canada (D/M/Y): ______/_____/_____
   
   Date returned in Canada (D/M/Y): ______/_____/_____
   
   Reasons for travel (check all that apply):
   - [ ] Visiting friends/relatives  [ ] Volunteer/missionary
   - [ ] Business  [ ] Education  [ ] Vacation
   - [ ] Medical tourism  [ ] Immigration  [ ] Military
   - [ ] Other, specify: ____________________________

6. PREVENTION MEASURES
   
   Pre-travel advice sought: [ ] Yes  [ ] No
   
   If yes, with whom?:
   - [ ] GP/family physician  [ ] Travel medicine clinic
   - [ ] Other: ____________________________
   
   Insect precautions?: [ ] Yes  [ ] No  [ ] Unknown
   
   Was chemoprophylaxis...
   - Suggested?: [ ] Yes  [ ] No  [ ] Unknown
   - Prescribed?: [ ] Yes  [ ] No  [ ] Unknown
   - Used?: [ ] Yes  [ ] No  [ ] Unknown

   If used, chemoprophylaxis type:
   - [ ] Chloroquine  [ ] Doxycycline  [ ] Malarone
   - [ ] Mefloquine  [ ] Other (specify): ____________________________

   Adherence: Did they take the drug as prescribed (before, during, after travel, missed <2 doses)?
   - [ ] Yes  [ ] No  [ ] Unknown

7. PATIENT ILLNESS
   
   Date became ill (D/M/Y): ______/_____/_____
   
   Date of 1st physician visit (D/M/Y): ______/_____/_____
   
   Was the patient admitted to hospital?: [ ] Yes  [ ] No
   
   If yes, date admitted (D/M/Y): ______/_____/_____

   Date of request (D/M/Y): ______/_____/_____
   
   Test used (check all that apply): [ ] RDT  [ ] Thick smear
   - [ ] Thin smear  [ ] Other (specify): ____________________________

   Diagnosis lab-confirmed: [ ] Yes  [ ] No
   
   Percent parasitemia (initial): ____________________________ %
   
   Percent parasitemia (at start of IV therapy): ____________________________ %

8. Has the patient had other medical treatment for this episode of malaria?
   - [ ] Yes  [ ] No  [ ] Unknown

   If yes, specify what drug(s): ____________________________

   Who prescribed the drug?
   - [ ] MD in Canada  [ ] MD in country of acquisition
   - [ ] Self prescribed  [ ] Other (specify): ____________________________

9. Indication for use of IV antimalarial therapy (check all that apply):
   - [ ] Continued vomiting or unable to tolerate oral therapy (Note: if this is the only indication for IV therapy, then QUININE preferred)
   - [ ] Hyperparasitemia (>2% in non-immune, >5% in semi-immune)
   - [ ] Impaired consciousness or coma
   - [ ] Prostrating (unable to walk or sit up without assistance)
   - [ ] Multiple convulsions (>2 in 24hrs)
   - [ ] Respiratory distress (acidotic breathing)
   - [ ] Respiratory failure / Pulmonary edema / ARDS
   - [ ] Circulatory collapse / shock (SBP<80mmHg in adults and <50mmHg in children)
   - [ ] Acute kidney injury / renal failure (Cr >265µmol/L or >upper limit for age for children)
   - [ ] Jaundice (Total bilirubin >45µmol/L)
   - [ ] Abnormal spontaneous bleeding/DIC
   - [ ] Hypoglycemia (<2.2mmol/L)
   - [ ] Metabolic Acidosis / Acidemia (pH<7.25, HCO3<15mmol/L)
   - [ ] Severe anemia (Hb <70g/L in adults and <50g/L in children)
   - [ ] Hemoglobinuria (macroscopic)
   - [ ] Hyperlactataemia (lactate >5mmol/l)
   - [ ] Other (specify): ____________________________

10. The following refer to time taken to begin IV therapy and is used to establish where/why delays occur:

   a) Hours to contact individual responsible for dispensing IV malaria therapy through the Canadian Malaria Network (#hours):
   
   b) Hours from request until drug received by pharmacy (#hours):
   
   c) Hours from time received in pharmacy until drug administered (#hours):
   
   d) Comments/perceived reasons for delay(s), if any:

11. Other Comments: ____________________________

   Completed by: ____________________________
   
   Date: ______/_____/_____
   
   Tel #: ____________________________
   
   Email: ____________________________

Thank you very much for completing this form.

Please complete Form B (follow-up) and send it in.

Version: March 2017
PARENTERAL THERAPY FOR SEVERE MALARIA - FORM B
To be completed by the Attending Physician

1. Follow-up Visit Date (D/M/Y): ______/_____/_____

2. REQUESTING/ATTENDING PHYSICIAN
Name: ____________________________
Hospital/site: ____________________________ Province: ____________________________
City: ____________________________ Tel#: ____________________________ Email: ____________________________
Initials (first/middle/last): ____________________________ Date of birth (D/M/Y): ______/_____/_____
Sex: ☐ Male □ Female

3. PATIENT DEMOGRAPHICS
Initials (first/middle/last): ____________________________ Date of birth (D/M/Y): ______/_____/_____
Sex: ☐ Male □ Female

4. TREATMENT
Date diagnosed (D/M/Y): ______/_____/_____
Date IV drug requested (D/M/Y): ______/_____/_____
Drug requested (check all that apply):
☐ Artesunate ☐ Quinine
Date of 1st IV drug dose (D/M/Y): ______/_____/_____
Number of doses of IV drug administered: ______
Number of vials of IV drug used:
â€” Vials of US Artesunate* (US Product)
  LOT# ____________________________
â€” Vials of Chinese Artesunate* (Chinese Product)
  LOT# ____________________________
â€” Ampoules of Quinine
  LOT# ____________________________
Step-down therapy or second antimalarial
(please specify and give number of days of therapy):
☐ Clindamycin (#days): ____________________________
☐ Doxycycline (#days): ____________________________
☐ Malarone (#days): ____________________________
☐ Quinine oral (#days): ____________________________
☐ Other (specify): ____________________________ (#days): ____________________________

5. MALARIA OUTCOMES
Malaria complications developed during admission
(check all that apply):
☐ Hyperparasitemia (>2% non-immune, >5% semi-immune)
☐ Impaired consciousness or coma
☐ Prostration (unable to walk or sit up without assistance)
☐ Multiple convulsions (>2 in 24hrs)
☐ Respiratory distress (acidotic breathing)
☐ Respiratory failure/Pulmonary edema/ARDS
☐ Circulatory collapse/shock (SBP<80mmHg in adults and <50mmHg in children)
☐ Acute kidney injury / renal failure (Cr >265μmol/L or >upper limit for age for children)
☐ Jaundice (Total bilirubin >45μmol/L)
☐ Abnormal spontaneous bleeding/DIC
☐ Hypoglycemia (<2.2mmol/L)
☐ Metabolic Acidosis/Acidemia (pH<7.25, HCO3<15mmol/L)
☐ Severe anemia (Hb<70g/L in adults and <50g/L in children)
☐ Hemoglobinuria (macroscopic)
☐ Hyperlactataemia (lactate >5mmol/L)
☐ Hemolysis
☐ Sepsis (specify organism): ____________________________
☐ Multigorgan Failure
☐ Other (specify): ____________________________

Maximum parasitemia level recorded: ______
Days until negativesmear achieved: ______
Total number of days hospitalized: ______
Total number of days in ICU: ______
Supportive treatments:
☐ Dialysis, (#days): ____________________________
☐ Mechanical ventilation, (#days): ____________________________
☐ Blood transfusion, (#units): ____________________________
☐ Antibiotics (specify): ____________________________
☐ Other (specify): ____________________________

Patient outcome as of today (check all that apply):
☐ Alive
☐ Still hospitalized
☐ Discharged on date (D/M/Y): ______/_____/_____
☐ Deceased on date (D/M/Y): ______/_____/_____
Were there any complications or adverse events related to the IV antimalarial drug?: ☐ Yes ☐ No
If yes, please specify: ____________________________
________________________________________________________________________
________________________________________________________________________

6. CANADIAN MALARIA NETWORK EVALUATION
Is this program to provide IV malaria therapy helpful to you?: ☐ Yes ☐ No
Did you consult with a physician through the Canadian Malaria Network?: ☐ Yes ☐ No
If yes, was this a beneficial interaction?: ☐ Yes ☐ No
Comments: ____________________________
________________________________________________________________________
________________________________________________________________________
Suggestions to improve the program: ____________________________
________________________________________________________________________
________________________________________________________________________
Completed by: ____________________________
Date: _____/_____/_____
Tel #: ____________________________
Email: ____________________________

Thankyouverymuchforcompleting this form.
Your cooperation is greatly appreciated.

Form Version: March 2017
# CANADIAN MALARIA NETWORK

## SUSPECTED ADVERSE REACTION REPORT

<table>
<thead>
<tr>
<th>ATTENDING PHYSICIAN INFORMATION:</th>
<th>ADVERSE REACTION:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>Reaction Identified:</td>
</tr>
<tr>
<td>Position:</td>
<td>Date (dd/mm/yy):</td>
</tr>
<tr>
<td>Hospital:</td>
<td>Time:</td>
</tr>
<tr>
<td>Address:</td>
<td>Reaction Resolved:</td>
</tr>
<tr>
<td>Phone:</td>
<td>Date (dd/mm/yy):</td>
</tr>
<tr>
<td>Fax:</td>
<td>Time:</td>
</tr>
<tr>
<td>Email:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENT INFORMATION:</th>
<th>Outcome(s) attributed to adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initials:</td>
<td>(Select all that apply)</td>
</tr>
<tr>
<td>Date of Birth (dd/mm/yy):</td>
<td>Death</td>
</tr>
<tr>
<td>Age:</td>
<td>Congenital malformation</td>
</tr>
<tr>
<td>Sex: M FEMAILE:</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>Country of Birth:</td>
<td>Required Intervention to prevent damage/impairment</td>
</tr>
<tr>
<td>Country of Residence:</td>
<td>Hospitalization – prolonged</td>
</tr>
<tr>
<td>Country(ies) of Acquisition:</td>
<td>Disability or incapacity</td>
</tr>
<tr>
<td>1)</td>
<td>Other:</td>
</tr>
<tr>
<td>2)</td>
<td></td>
</tr>
<tr>
<td>3)</td>
<td></td>
</tr>
<tr>
<td>Is the country of acquisition chloroquine resistant?</td>
<td>Yes, No, Unknown</td>
</tr>
</tbody>
</table>

Medical history and pre-existing medical conditions (e.g. allergies, pregnancy, smoking/alcohol use, renal dysfunction, etc.)

Regular medications (excluding new agents administered during admission):

<table>
<thead>
<tr>
<th>MALARIA DIAGNOSIS &amp; TREATMENT:</th>
<th>SUSPECTED DRUG(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First medical visit</td>
<td>Suspected Drug Name &amp; Strength:</td>
</tr>
<tr>
<td>Date (dd/mm/yy):</td>
<td>Drug Lot #:</td>
</tr>
<tr>
<td>Time:</td>
<td>Total #:</td>
</tr>
<tr>
<td>Malaria Diagnosis Start</td>
<td>Route(s) of Administraion:</td>
</tr>
<tr>
<td>Date (dd/mm/yy):</td>
<td></td>
</tr>
<tr>
<td>Time:</td>
<td></td>
</tr>
<tr>
<td>Type of Smear Used:</td>
<td>Manufacturer Name &amp; Address:</td>
</tr>
<tr>
<td>RDT</td>
<td>MFR Control #:</td>
</tr>
<tr>
<td>Thick</td>
<td>Pharmacy Name &amp; Address:</td>
</tr>
<tr>
<td>Thin</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
<tr>
<td>Parasitemia %:</td>
<td></td>
</tr>
<tr>
<td>Malaria Treatment Start</td>
<td>Therapy Start:</td>
</tr>
<tr>
<td>Date (dd/mm/yy):</td>
<td>Date (dd/mm/yy):</td>
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<tr>
<td>Time:</td>
<td>Time:</td>
</tr>
<tr>
<td>Malaria Treatment End:</td>
<td>Therapy End:</td>
</tr>
<tr>
<td>Date (dd/mm/yy):</td>
<td>Date (dd/mm/yy):</td>
</tr>
<tr>
<td>Time:</td>
<td>Time:</td>
</tr>
<tr>
<td>Malaria Complications:</td>
<td>Total doses administered until first sign / symptom of reaction:</td>
</tr>
<tr>
<td></td>
<td>Time between first administration and first reaction sign / symptom:</td>
</tr>
</tbody>
</table>

Malaria Treatment Procedures / Drugs Administered (excluding those used to treat reaction): (name, dose/#units, frequency, dates)

**Submit this form within 24 hours by email to** [CanadianMalariaNetwork@toh.on.ca](mailto:CanadianMalariaNetwork@toh.on.ca), or by fax to 613-737-8164. **Version: March 2017**