Canadian Malaria Network
Réseau canadien sur le paludisme

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 613-761-5260.

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

GUIDELINES FOR THE TREATMENT OF MALARIA

The following guidelines have been adapted from the 2014 Canadian Recommendations for the Prevention and Treatment of Malaria. Canada Communicable Disease Report, 2014 Available at: http://www.phac-aspc.gc.ca/tmp-pmv/prof-eng.php and 2018 recommendations (in press).

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 treatment varies according to the species of malaria. Falciparum species usually causes the most severe disease and is a medical emergency.
2. **Is this a severe or complicated infection?** This can be determined using the table below. The presence of any **one** of the listed criteria defines severe malaria. 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 2014 (http://www.phac-aspc.gc.ca/tmp-pmv/prof-eng.php).

CRITERIA FOR SEVERE MALARIA

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

ARDS: acute respiratory distress syndrome; *AKI: acute kidney injury*

Hyperparasitemia 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 years

*Non-immune = those born in non-endemic countries or low-transmission settings, such as travellers.

**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.

From: 2014 and 2018 Canadian Recommendations for the Prevention and Treatment of Malaria; CCDR 2014 and in press; World Health Organization. Management of Severe Malaria: A Practical Handbook. 3rd ed. WHO, Geneva 2012 (Available at: http://www.who.int/malaria/publications/atoz/9789241548526/en/index.html); World Health Organization. Guidelines for the treatment of malaria. 3rd ed. WHO. Geneva, 2015.

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 can have a mortality rate of up to 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 parenteral (intravenous) artesunate or parenteral 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 quinine IV. ***Due to the limited supply of artesunate IV, quinine IV 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 additional agents, usually administered orally, as follow-on therapy. Atovaquone/proguanil (Malarone®) is the preferred agent unless contraindicated; quinine with either doxycycline or clindamycin are alternatives. For assistance with treatment of severe malaria, please consult Chapter 7 of the 2014 Canadian Recommendations for the Prevention and Treatment of Malaria 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.

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 ARTESUNATE:

- 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. hypo-glycaemia) 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 B" 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 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.

INTRAVENOUS 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 ºC.
Buffer may be stored at 2-30 ºC (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℃. 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).

Product Expiration Date:

US product (Walter Reed supply): Artesunate vials currently do not have a specified expiry date, as testing of the product is ongoing.

Chinese product (Artesun®): As per package.

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 into an established IV line immediately following reconstitution of drug.
The patient may be switched to oral therapy *after a minimum of 24 hours (3 doses)* of artesunate IV 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 4 weeks following treatment with artesunate.**
- Dose adjustment of artesunate is not required in renal or liver dysfunction.
- **Pregnancy:** Artesunate IV is preferred over quinine IV for the treatment of severe malaria in all trimesters of pregnancy.
- 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 artesunate's short half-life (< 2 hours), malaria can recrudesce following treatment with artesunate IV within days to weeks unless treatment is followed with a longer acting agent. Thus, follow-on therapy with oral antimalarial agents is essential, and should be started 4 hours after the last artesunate IV 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, oral antimalarial therapy is required as follow-on therapy (see below). The oral agent(s) should be started 4 hours after the last dose of artesunate IV. Malarone® is the preferred agent (unless patient had received prophylaxis with Malarone,® is pregnant, or CrCl <30 ml/min); oral quinine# with either 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 doxycycline IV (100 mg Q12H or 2 mg/kg Q12H (max 100 mg) for pediatric (≥ 8 years old) patients; Special Access drug) or clindamycin IV (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.

#**Note**: if 4 doses of IV artesunate are administered (as opposed to switching to oral after 3 doses if the patient can tolerate oral at that time), then doxycycline or clindamycin alone (without quinine) may be used as follow-on therapy in cases where Malarone® is not an appropriate follow-on option.

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

Oral Antimalarial Agents: Recommended Drug Doses

DRUG	ADULT DOSE	PEDIATRIC DOSE
Malarone® (Atovaquone/Proguanil) **Adult tablet:** Atovaquone 250 mg/Proguanil 100 mg per tablet **Pediatric tablet:** Atovaquone 62.5 mg/Proguanil 25 mg per tab	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
Quinine sulphate (**Note**: quinine sulphate 600 mg = 500 mg quinine base)	600 mg orally Q8H for 7 days	9 mg/kg orally Q8H for 7 days (max 600 mg/dose)
Doxycycline (**Note:** Contraindicated in pregnancy, breastfeeding, and age < 8 years)*	100 mg BID for 7 days	2 mg/kg (to a maximum of 100 mg) BID for 7 days
Clindamycin (**Note:** use only if unable to take Malarone® or doxycycline)	300 mg q6h for 7 days	5 mg/kg every 6 hours for 7 days

* While doxycycline is contraindicated during pregnancy, it may be used during breastfeeding and in children < 8 years of age for the treatment of malaria if other options (i.e., Malarone® and clindamycin) are not possible.

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 parasitemia 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 artesunate IV 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:

Note: mg/kg dosage is the same for children and adults
Base dose on ideal body weight (IBW) in obesity

LOADING DOSE:

Requires administration via IV pump:

- Quinine dihydrochloride 7 mg/kg IBW (equivalent to 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 within the proceeding 24 hours, or a dose of mefloquine within the preceding two weeks 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 IBW (equivalent to quinine base 8.3 mg/kg)
- Diluted in 10 mL/kg of isotonic fluid (D5W preferred) by intravenous infusion over 4 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 and patient remains severely ill or continues to have acute renal injury, change dosing interval to Q12H after 48hrs. Full dose can be continued if patient is receiving dialysis.

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 artesunate IV, quinine IV 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:

Cinchonism (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, haemoglobiuria, 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 quinine IV or as soon as possible when 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,® is pregnant, 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

DRUG	ADULT DOSE	PEDIATRIC DOSE
Malarone® (Atovaquone/Proguanil) **Adult tablet:** Atovaquone 250 mg/Proguanil 100 mg per tablet **Pediatric tablet:** Atovaquone 62.5 mg/Proguanil 25 mg per tab	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
Quinine sulphate (**Note**: quinine sulphate 600 mg = 500 mg quinine base)	600 mg orally Q8H for 7 days	9 mg/kg orally Q8H for 7 days (max 600 mg/dose)
Doxycycline (**Note:** Contraindicated in pregnancy, breastfeeding, and age < 8 years)*	100 mg BID for 7 days	2 mg/kg (to a maximum of 100 mg) BID for 7 days
Clindamycin (**Note**: use only if unable to take Malarone® or doxycycline)	300 mg q6h for 7 days	5 mg/kg every 6 hours for 7 days

* While doxycycline is contraindicated during pregnancy, it may be used during breastfeeding and in children < 8 years of age for the treatment of malaria if other options (i.e., Malarone® and clindamycin) are not possible.

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 hypoglycemia, 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, pregnant women 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. Severe or complicated malaria caused by *P. falciparum*:
   - Artesunate IV (**total of four doses recommended)**, followed by a 7-day course of clindamycin

Notes:

- Full doses of all antimalarials should be used in pregnant patients.
- Artesunate is now recommended as first line treatment for severe malaria in all trimesters of pregnancy. Quinine IV may be used if artesunate is not tolerated or not available. Quinine IV should be used in preference to artesunate IV for the management of non-severe malaria when oral therapy is not tolerated, as recommended for the general population. Oral therapy with quinine plus clindamycin should be substituted as soon as the patient can tolerate medication.
- 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.

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The Ottawa Hospital | L'Hôpital d'Ottawa

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

The Ottawa Hospital | L'Hôpital d'Ottawa
RESEARCH INSTITUTE | INSTITUT DE RECHERCHE

Canadian Malaria Network
Réseau canadien sur le paludisme

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: _____

Drug Name	Quantity on Hand	Quantity Requested
Artesunate 110 mg vials (US Product)		
Phosphate Buffer 12 ml vials (if USA supply)		
Artesunate 120 mg vials (Chinese Product)		
Quinine Dihydrochloride 600 mg / 2 mL ampoules		

PLEASE complete the following table:

DISPENSING(S) SINCE YOUR LAST SHIPMENT			
Drug Name	Date Dispensed (dd/mm/yy)	Quantity of vials/ Ampoules Issued to Subject OR Site	Lot # Used

Please fax to 613-761-5260 or email to CanadianMalariaNetwork@toh.ca

Parenteral artesunate and quinine are provided by Health Canada's Special Access Program through the Canada Malaria Network (CMN)

Version: December 2017

Canadian Malaria Network
Réseau canadien sur le paludisme

CMN ID: _____

CANADIAN MALARIA NETWORK

PHARMACY DISPENSING RECORD FOR IV-ARTESUNATE & IV-QUININE

REQUESTING AND/ OR ATTENDING PHYSICIAN (Physician information only)

Physician Name: _____ Department:: _____
Hospital: _____ Telephone: _____
City: _____ Fax: _____
Province: _____ Email: _____
(REQUIRED)

PATIENT INFORMATION

Local Hospital Identification Number: _____
Initials (first/middle/last): _____
Date of Birth (dd/mm/yy): _____
Weight: _____ Kg

Sex: Male ☐ Female ☐ If female, is patient pregnant: Yes ☐ No ☐ Unknown ☐

PHARMACY DISPENSING SITE

City: _____
Hospital: _____

Prescribing Physician and/or Contact have consulted with an Infectious Disease Physician? : Yes ☐ No ☐ Unknown ☐

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 (with information package and mandatory CMN forms - **Form A & Form B**)

☐ Artesunate + Phosphate buffer diluent (US Product)
Vials: _____ Lot #: AA-241-1-10-01
Vials: _____ Lot #: 2097- 16

☐ Artesunate with bicarb pre-packaged (Aretsun® , Chinese Product)
Vials: _____ Lot #: _____

☐ Quinine (one kit of 7 ampoules) expiry 02/ 2019
Ampoules: _____ Lot #: _____

METHOD OF SHIPPING/ARRANGEMENTS (pick-up and delivery)

(Note: Artesunate Lot # AA-241-1-10-01 must be shipped as a refrigerated item) _____

_____

_____

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

Version: December 2017

Complete and return to the CMN Coordinating Centre within 24 hours of dispensing by e-mail: CanadianMalariaNetwork@toh.on.ca or by Fax: 613-761-5260

Parenteral artesunate and quinine are provided by Health Canada's Special Access Program through the Canada Malaria Network (CMN)

CANADIAN MALARIA NETWORK

CMN ID: _____

FORM A- MANDATORY INITIAL ASSESSMENT FORM

To be completed by the Attending Physician with use of parenteral therapy for severe malaria

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

2. Drug requested (check all that apply):
   - ❑ US Artesunate* (USA Product) LOT# AA-241-1-10-01
   - ❑ 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: _____(required)

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):_____/____/_____

8. DIAGNOSIS
   Diagnosis lab-confirmed: ☐ Yes ☐ No
   Date (D/M/Y):_____/___/_____
   Test used (check all that apply): ☐RDT ☐Thick smear
   ☐Thin smear ☐Other (specify):_____

   Malaria species (check all that apply):
   - ❑ P. falciparum ☐ P. vivax ☐ P. malariae
   - ❑ P. ovale ☐ P. knowlesi ☐ Unknown

   Percent parasitemia (initial): _____%
   Percent parasitemia (at start of IV therapy):_____%

9. 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):_____

10. 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 (i.e., ≥2% in children <5 yrs; older children & adults: ≥5% if non-immune; ≥10% if 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)
    - ❑ Other (specify):_____

11. 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:
    _____

12. 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: December 2017

Please complete and return to the CMN Coordinating Centre within 24 hours of starting IV drug treatment by e-mail: canadianmalarianetwork@toh.on.ca or by fax: 613-761-5260.

Parenteral artesunate and quinine are provided by Health Canada's Special Access Program through the Canada Malaria Network (CMN)

CMN ID: _____

CANADIAN MALARIA NETWORK

FORM B- MANDATORY FOLLOW UP FORM

To be completed by the Attending Physician following the use of parenteral therapy for severe malaria

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

2. REQUESTING/ATTENDING PHYSICIAN
   Name: _____
   Hospital/site:_____
   City: _____ Province:_____
   Tel#:_____Fax#:_____
   Email: _____(required)

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:
   _____ Vials of US Artesunate*(US Product)
   Lot AA-241-1-10-01
   _____ Vials of Chinese Artesunate* (Chinese Product)
   (Lot#_____)
   _____ 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 (i.e., ≥2% in children <5 yrs; older children & adults: ≥5% if non-immune; ≥10% if 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/ <50g/L in children)
   - ❑ Hemoglobinuria (macroscopic)
   - ❑ Hyperlactataemia (lactate >5mmol/l)
   - ❑ Hemolysis
   - ❑ Sepsis (specify organism):_____
   - ❑ Multiorgan Failure
   - ❑ Other (specify):_____

   Maximum parasitemia level recorded:_____%
   Days until negative smear 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 complete the CMN Suspected Adverse Reaction Form and briefly specify event below:_____
   _____
   _____
   _____
   _____

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:_____
   _____
   _____

   Other Comments:_
   _____

   Completed by:_____
   Date: _____/_____/_____Tel #:_
   _____

   Email:_____

Version: December 2017

Please complete and return to the CMN Coordinating Centre on day 7 following start of IV drug treatment by e-mail: canadianmalarianetwork@toh.on.ca or by fax: 613-761-5260

Parenteral artesunate and quinine are provided by Health Canada's Special Access Program through the Canada Malaria Network (CMN).

CANADIAN MALARIA NETWORK

SUSPECTED ADVERSE REACTION REPORT

CMN ID: _____

ATTENDING PHYSICIAN INFORMATION:

Name:	
Position:	
Hospital:	
Address:	
Phone:	**Fax:**
Email:	(required)

PATIENT INFORMATION:

Initials:	**Date of Birth** (dd/mm/yy):	**Age:**	**Sex:** ❑M ❑F

Country of Birth:

Country of Residence:

Country(ies) of Acquisition:
1) 2) 3)

Is the country of acquisition chloroquine resistant?
❑Yes ❑No ❑Unknown

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):

MALARIA DIAGNOSIS & TREATMENT:

First medical visit Date (dd/mm/yy):	Time:	**Malaria Diagnosis** Date (dd/mm/yy):	Time:

Type of Smear Used:
❑RDT ❑Thick ❑Thin
❑Other:

Plasmodium Species:
❑P.falciparum ❑P.ovale
❑P.knowlesi ❑P. vivax
❑P.malariae ❑Unknown

Parasitemia %:

Malaria Treatment Start Date (dd/mm/yy):	Time:	**Malaria Treatment End** Date (dd/mm/yy):	Time:

Malaria Complications:

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

ADVERSE REACTION:

Reaction Identified: Date (dd/mm/yy):	Time:	**Reaction Resolved:** Date (dd/mm/yy):	Time:

Outcome(s) attributed to adverse reaction
(Select all that apply)
❑Death
❑Life-threatening
❑Hospitalization – prolonged
❑Disability or incapacity
❑Congenital malformation
❑Required Intervention to prevent damage/impairment
❑Other:

Describe reaction or event:

Relevant tests/laboratory data:

Treatment of reaction (name, dose, frequency, dates)

SUSPECTED DRUG(S)

Suspected Drug Name & Strength:	**Drug Lot #**	**Total # Dose(s):**	**Route(s)of Administration:**

Manufacturer Name & Address	**MFR Control #:**	**Pharmacy Name & Address**

Therapy Start Date (dd/mm/yy):	Time:	**Therapy End** Date (dd/mm/yy):	Time:

Total doses administered until first sign / symptom of reaction:

Time between first administration and first reaction sign / symptom:

Action taken with drug:
❑Reduced ❑Treatment Complete
❑Withdrawn ❑Other
❑Unchanged

Reaction abated after use stopped or dose reduced:
❑Yes ❑No ❑NA

Did reaction reappear after drug reintroduction?
❑Yes ❑No ❑Drug not reintroduced

SUBMISSION

Name:	Date:

Submit this form within 24 hours by email to CanadianMalariaNetwork@toh.on.ca, or by fax to 613-761-5260

Parenteral artesunate and quinine are provided by Health Canada's Special Access Program through the Canada Malaria Network (CMN)