STH Artesunate Guidelines

Artesunate is the drug of choice for treatment of severe malaria and cerebral malaria due to P.falciparum (see attached document for monograph).

Artesunate is a special access medication and is supplied to designated hospitals through the Canadian Malaria Network. At Stanton we are a satellite pharmacy of U of A and as such we are permitted to keep a ready supply on hand. Stanton Hospital shall maintain a supply of artesunate sufficient to treat a 100kg individual.

When resupply is needed, contact U of A Pharmacy at 780-407-1586 to place an order. We must arrange for a pick up via Buffalo Airlines or any another suitable alternative.

When artesunate is dispensed the physician must complete two forms. Form A must be submitted within 48 hours of use, and Form B must be completed on day 7. Paperwork is not to be filed with Health Canada. Both forms are sent to Dr. McCarthy at the Canadian Malaria Network in Ottawa. The address is as follows:

The Ottawa Hospital
501 Smyth Rd
Ottawa, ON
K1H 8L6

A log of artesunate dispensed should be kept by pharmacy. The Canadian Malaria Network may contact us to determine details of our usage (see attached document for sample log).
Lab must send malaria specimens to Dr. Kevin Kain in Toronto. He carries out testing on malaria isolates. The attached document has a FedEx number and shipping instructions.

At this time we are not billed for artesunate.

Any queries regarding the Malaria Program should be directed to the research group prxstudytechs@toh.on.ca or phone 613-737-8970.

INTRODUCTION TO THE CANADIAN MALARIA NETWORK

You have access to parenteral therapy for malaria treatment. You are receiving either intravenous ARTESUNATE or intravenous QUININE. This package has been designed to assist you with patient care and use of these drugs.

If required, assistance is always available through Canadian Malaria Network participants listed at www.travelhealth.gc.ca.

Please note that these drugs are provided through the courtesy of Health Canada's Special Access Program, and therefore you are responsible for filling out reporting form A (within 48hrs of receiving drug) and form B (on day 7). 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 network or replenishing your stock please contact us through the coordinating center e-mail at: canadianmalarianetwork@toh.on.ca.

This package also includes directions for shipping malaria specimens to the Laboratory of Dr. Kevin Kain in Toronto. Dr. Kain has received funding to carry out laboratory testing of malaria isolates, and has a particular interest in drug resistance in Canadian malaria isolates. He requests that you ship specimens of all new malaria cases to his laboratory for evaluation. Please see the shipping instructions page, enclosed, for shipping and contact information. Please note that Dr. Kain has supplied a FedEx number so that the shipping can be carried out free of charge.

INTRODUCING ***ARTESUNATE***—
A NEW PARENTERAL AGENT FOR THE TREATMENT OF SEVERE MALARIA

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

Artesunate is recommended by the World Health Organization as ***treatment of choice*** for severe and complicated malaria, or for patients who cannot tolerate oral therapy.
IV artesunate will replace the use of IV quinine for most patients requiring parenteral therapy for the management of malaria.

Some 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. hypoglycaemia) than IV quinine.
- Occasional side effects include anorexia, dizziness, lightheadedness, headache, taste alteration, nausea, diarrhea, reversible decrease in reticulocyte count, increased liver enzymes, bradycardia, rare allergic reactions (urticaria, pruritis, dyspnea).
- 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).
- 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 supply is provided by the Walter Reid Army Institute of Research (WRAIR) in the USA.
- The CMN National coordinating centre has a new email address: **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 2009 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

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:	Artesunate 110 mg/vial; sterile powder with diluent (phosphate buffer) for reconstitution.
Storage:	Store at 2-10 ^{o}C. Buffer may be stored at 2-30 ^{o}C (note: phosphate crystals may form in the buffer at lower temperatures; these will dissolve if gently warmed)
Reconstitution:	Reconstitute 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.
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:	No data.
Product Expiration Date:	Artesunate vials currently do not have a specified expiry date, as testing of the product is ongoing.

Dosage/Administration for Severe Falciparum Malaria:

Currently, a 4-dose regimen of intravenous artesunate is recommended: 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). 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 drug may be mixed with 5 mL of 5% dextrose or normal saline prior to injection if desired. The same weight based dosing regimen is used for pediatric patients.

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)
- 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.
- 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, and should be started 4 hours after the last IV artesunate dose.
- Artesunate has been administered intramuscularly if venous access is not possible.
- 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), with doxycycline or clindamycin as 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 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.

FOLLOW-ON ORAL THERAPY:

Start either a 3-day course of Malarone® tablets* (preferred) or a 7-day course of doxycycline or clindamycin.

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
Doxycycline **(Note:** Contraindicated if age < 8 years, during pregnancy or breastfeeding)	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)	20 mg/kg/day orally, divided into 3 or 4 doses, for 7 days	20 mg/kg/day orally, divided into 3 doses, for 7 days

Artesunate Adverse Effects:

Artesunate is very well tolerated in adults and children. Occasional side effects include anorexia, dizziness, lightheadedness, taste alteration, nausea, diarrhea, reversible decrease in

reticulocyte count, increased liver enzymes, bradycardia, heart block, and rare allergic reactions (e.g. urticaria, pruritis, dyspnea)

Manufacturer: SRI International
Menlo Park, California
USA

References:

Committee to Advise on Tropical Medicine and Travel (CATMAT). Canadian Recommendations for the prevention and treatment of malaria among international travelers. CCDR 2009;35S1:1-82.

World Health Organization. Guidelines for the Treatment of Malaria. 2006. WHO, Geneva, available at http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf

Griffith KS, Lewis LS, Mali S, Parise, ME. Treatment of Malaria in the United States. A Systematic Review. JAMA 2007;297:2264-77.

Intravenous Artesunate for the Treatment of Severe Malaria in the United States. IND Protocol # 76,725 Investigational Brochure. June 21, 2007

Rosenthal PJ. Artesunate for the treatment of severe falciparum malaria. N Engl J Med. 2008 Apr 24;358(17):1829-36.

Dondorp A, Nosten F, Stepniewska K, Day N, White N; South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet. 2005;366:717-25.

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

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^{o}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:

ii. Loading Dose (L.D.)

If IV Pump Available:

- 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 L.D.

*If IV Pump **Not** Available:*

- Quinine dihydrochloride 20 mg salt/kg OR quinine 16.7 mg base/kg
- Diluted in 10 mL/kg of isotonic fluid (D5W preferred) by intravenous infusion over 4 hours, then start maintenance dose.
- Commence maintenance dose 8 hours after L.D. (12 hours for children).

L.D. SHOULD NOT BE USED if patient received quinine or quinidine within the preceding 24 hours or mefloquine in previous 2 weeks. Maintenance dosing should be used for these patients.

iii. Maintenance Dose (M.D.)

- 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 4 hours.

- Repeat every 8 hours (in adults) or 12 hours (in children) until indication (e.g. % parasitemia) for IV quinine therapy no longer exists and/or patient can swallow, then switch to oral therapy to complete treatment course (see page 2).
- If patient requires more than 48 hours of parenteral therapy, reduce quinine maintenance dose by one third to one half (i.e. 5-7 mg/kg of the dihydrochloride salt) to avoid accumulation

Additional Information:

- Intravenously, the drug should be given slowly (over 4 hours) to avoid the risk of cardiovascular toxicity; pulse and blood pressure should be closely monitored and the rate of infusion attenuated if dysrhythmias occur.
- Replace with oral therapy (quinine sulfate 600 mg PO Q8H--adult dose) as soon as possible.
- 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, asthma precipitated, 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 and/or base any dosage reduction on serum quinine levels.

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 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** doxycycline or clindamycin to complete 7 day course.

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

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
Doxycycline **(Note:** Contraindicated if age < 8 years, during pregnancy or breastfeeding)	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)	20 mg/kg/day orally, divided into 3 or 4 doses, for 7 days	20 mg/kg/day orally, divided into 3 doses, for 7 days

Manufacturer: Formulations PLC
9 Royal Parade
Key Gardens, Surrey
England, T29 3QD

GUIDELINES FOR THE TREATMENT OF MALARIA

The following guidelines have been adapted from the 2009 Canadian Recommendations for the Prevention and Treatment of Malaria among International Travellers. Canada Communicable Disease Report, Supplement – (www.hc-sc.gc.ca/hpb/lcdc/publicat/ccdr).

a. 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.
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 2009 (www.hc-sc.gc.ca/hpb/lcdc/publicat/ccdr).

Criteria for severe falciparum malaria

Clinical manifestation	Laboratory test
Prostration/impaired consciousness	Severe anaemia (haematocrit < 15%; Hb < 50 g/L)
Respiratory distress	Hypoglycaemia (blood glucose < 2.2 mmol/L)
Multiple convulsions	Acidosis (arterial pH < 7.25 or bicarbonate < 15 mmol/L)
Circulatory collapse/shock	Renal impairment (creatinine > 265 umol/L)
Pulmonary oedema (radiological)	Hyperlactataemia
Abnormal bleeding	Hyperparasitaemia (≥ 5%)
Jaundice	
Haemoglobinuria (macroscopic)	

From: 2009 Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers

b. 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. 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, with doxycycline or clindamycin as alternatives. For assistance with treatment of severe malaria, please consult Chapter 7 of the 2009 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. 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 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 artesunate, 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:

1. World Health Organization. Guidelines for the Treatment of Malaria. 2006. WHO, Geneva, available at http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf
2. Treatment of Malaria (Guidelines for Clinicians). Centers for Disease Control and Prevention. Website: http://www.cdc.gov/malaria/diagnosis_treatment/tx_clinicians.htm
3. Nosten F, McGready R, Mutabingwa T. Case management of malaria in pregnancy. Lancet Infect Dis

MALARIA SHIPPING DIRECTIONS:

IN ALL MALARIA CASES PLEASE SEND:

i. thick and thin smears (if available)

ii. any amount of residual blood (in EDTA/purple top or ACD/yellow top or clotted blood) at room temperature by overnight courier (PREFERRED ROUTE). If this is not possible within 72-96 hrs, then freeze blood at – 20 degrees and send on dry or wet ice/freezer packs at your convenience.

TO: Kevin Kain MD, FRCPC
Tropical Disease Unit
Toronto General Hospital, EN G-224
200 Elizabeth Street
Toronto, Ontario M5G 2C4
416-340-3535 fax 416-595-5826
Kevin.Kain@uhn.on.ca

iii. Use my FedEx number: # 2391-4007-6 and check bill recipient on the shipping form.

PARENTERAL DRUG THERAPY MANUAL	NAME OF MEDICATION **ARTESUNATE ***
OTHER NAMES	CLASSIFICATION Antimalarial

INDICATIONS

- Treatment of severe and complicated malaria due to *Plasmodium falciparum.*
- Treatment of non complicated malaria in patients unable to take oral therapy.

ADMINISTRATION

- Reconstitute each vial of 110 mg of artesunate base by slowly injecting (against vial wall) 11 mL of the provided phosphate buffer diluent to get a concentration of 10 mg/mL. Gently swirl for 5 to 6 minutes.
- IV direct: administer over 1-2 minutes into the tubing of a freely running IV solution of D5W or NS.
- IM (if IV access cannot be obtained).
- Administer dose within 60 minutes of reconstitution.
- Observe patient for 30 minutes following administration for signs of a hypersensitivity reaction.

POTENTIAL ADMINISTRATION HAZARDS

- Hypersensitivity (rare): rash, urticaria, itching, swelling, watery eyes, shortness of breath, chest pain, anaphylaxis.
- Cardiovascular: bradycardia.
- GI: anorexia, nausea, vomiting, diarrhea, taste alteration.
- CNS: dizziness, lightheadedness, headache.
- Reversible decrease in reticulocyte count.
- Increased liver enzymes.

DOSAGE

- 2.4 mg/kg at 0, 12, 24 and 48 hours (total of 4 doses or 9.6 mg/kg). First dose should be administered STAT.
- No dosage adjustment required in patients with renal or hepatic impairment.
- Obese patients should be dosed based on actual body weight (i.e., no maximum dose).

COMPATIBILITY, STABILITY

- Store unreconstituted vial at 2-10°C.
- Phosphate buffer diluent may be stored at 2-30°C; in colder temperatures, phosphate crystals or precipitate may form; these will dissolve if gently warmed. Diluent should only be used if solution is clear and colourless after warming.
- Stable 60 minutes after reconstitution. Discard any unused solution.

MISCELLANEOUS

- Follow-on therapy with a second agent (e.g., combination of atovaquone and proguanil [Malarone ®], doxycycline, or clindamycin) is essential, and should be started at least 4 hours after the last dose of artesunate.

REFERENCES

115, 168, 553, 554, 555, 556.

* Available via the Health Canada Special Access Program through the Canadian Malaria Network