Artesunate
Powder and diluent for reconstitution 60mg

Guidance for individual patient approval
Last updated December 2010

Note: The QHMAC approved the addition of artesunate to the Queensland Health List of Approved Medicines (LAM) in 2006 following trial evidence that it was the most optimal therapy for severe falciparum malaria. It should only be used in specific cases where Individual Patient Approval (IPA) is obtained, as artesunate does not have marketing approval in Australia. **This guide has been drafted to assist medical superintendents (or delegates) and local medicines committees in their consideration of IPA requests. Initiation of therapy should be on the advice of an infectious diseases physician.**

IPA indication

For the treatment of severe falciparum malaria.

Background

Artemisinin, also known as qinghaosu, is a sesquiterpene lactone extracted from the leaves of *Artemisia annua* (sweet wormwood), used in China for treatment of fever for over a thousand years. It is a potent and rapidly acting blood schizontocide and is active against all Plasmodium species. It has an unusually broad activity against asexual parasites, killing all stages from young rings to schizonts. In P. falciparum malaria, artemisinin also kills the gametocytes—including the stage 4 gametocytes, which are otherwise sensitive only to primaquine.

Various artemisinin derivatives have been used in the treatment of severe malaria including artemether, artemisinin (rectal), artemotil and artesunate. Artesunate is a derivative of dihydroartemisinin which is a more potent form of artemisinin. It is converted to dihydroartemisinin in vivo and has superior physicochemical properties to artemether and artemotil as it is water soluble and can be given either by intravenous or intramuscular injection.

TGA approved indications

Parenteral artesunate does not have marketing approval in Australia and there is currently no manufacturer who can produce a formulation compliant with Australian Good Manufacturing Practice (GMP) specifications.

Pending availability of a GMP-compliant product which can be registered in Australia, the Therapeutic Goods Administration (TGA) allows importation of artesunate for Category A use in patients with severe malaria under the Special Access Scheme (SAS). SAS Category A patients are defined in the legislation as “persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment”.

Central Pharmacy has a limited supply of a World Health Organization (WHO) qualified Chinese brand of artesunate 60mg injection which is imported by Link Pharmaceuticals. Due to its SAS requirement and limited availability, a small quantity of emergency stock is to be held in a few selected hospitals. Subsequent supplies will only be provided by Central Pharmacy upon presentation of a completed Category A SAS form, which must be forwarded to Central Pharmacy (Fax no: 07 3120 8561) each time the drug is ordered.

As artesunate is not registered in Australia, responsibility for its use rests primarily with the medical practitioner and the patient. The medical practitioner should obtain informed consent from the patient or Statutory Health Attorney and also forward a copy of the Category A SAS form to the TGA within 28 days of its completion.

Role in therapy

The WHO Guidelines for the Treatment of Malaria 2010 (2nd Ed)[1] support artesunate IV as the treatment of choice for adults with severe malaria.

As death from severe malaria often occurs within hours of admission to hospital, it is essential that antimalarial treatment is given in full doses as soon as possible to quickly achieve therapeutic concentrations.

Urgent treatment of severe malaria is essential if the patient has any of the following[2]:

- any degree of altered consciousness, jaundice, oliguria, severe anaemia or hypoglycaemia
- a parasite count above 100,000/mm^3 (>2% of red blood cells parasitised)
- the patient has intractable vomiting or is clinically acidotic.

Chloroquine-resistant *Plasmodium falciparum* must be assumed to be the infective agent. Once mandatory IV therapy has been started, seek expert advice. A recent large multicentre randomised controlled trial has shown that mortality in severe *P. falciparum* malaria is lower when IV artesunate is used rather than IV quinine.

Artesunate should be used in preference to IV quinine, if it is immediately available. **Use artesunate 2.4 mg/kg IV bolus on admission and repeat at 12 hours and 24 hours, then once daily until oral therapy is possible.** When the patient is able to tolerate oral therapy, give a full course of artemether + lumefantrine 20mg/120mg – i.e. six doses of four tablets (total course of 24 tablets) given over a period of 60 hours, as for uncomplicated *Plasmodium falciparum* malaria.

To ensure oral therapy can be administered as soon as possible, hospitals holding emergency stock of parenteral artesunate should also hold stock of artemether + lumefantrine (Riamet®) tablets which can be ordered through Central Pharmacy via the normal process.

If parenteral artesunate is not immediately available, IV quinine dihydrochloride should be used without delay as per Therapeutic Guidelines Antibiotic 2010 14th Edition. All Queensland hospitals are required to hold emergency stocks of IV quinine, even if they are also holding Artesunate stocks.

It is recommended that, in considering individual patient approval requests, medical superintendents (or delegates) should give favourable consideration to the use of artesunate for the treatment of severe plasmodium falciparum malaria in accordance with the above regimen, based on the Therapeutic Guidelines Antibiotic 2010 14th edition.

Initiation of therapy should be on the advice of an infectious diseases physician.

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[1] World Health Organisation (WHO) Guidelines for the Treatment of Malaria 2010. Available at http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html.
[2] Editors, *Therapeutic Guidelines: Antibiotic Version 14*, 2010. North Melbourne: Therapeutic Guidelines Ltd.
[3] Dondorp A, Nosten F, Stepniewska K, Day N, White N for the South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *The Lancet* 2005;366:717-25.

Safety

Adverse effects to artesunate are uncommon and few can be unequivocally linked to the drug, since they are often consistent with signs, symptoms or sequelae of malaria infection. Several million patients have been treated with an artemisinin drug, more than 10,000 of them as participants of clinical studies and at least 300 having formal neurophysiological evaluations, without any confirmed reports of neurotoxicity. The long gaps following initial doses, and the limited duration of treatment, may act as a safeguard against neurotoxicity.

There are no known contraindications to the use of artesunate. Pregnancy is not currently considered to be a contraindication to its use in severe malaria, although studies on its safety in pregnancy are still ongoing.

Evidence

Results from randomised trials in South-East Asia comparing artesunate and quinine show clear evidence of benefit with artesunate[1]. The largest trial was a randomised, controlled multi-centre trial (SEAQUAMAT study group: Bangladesh, India, Indonesia and Myanmar[3]) with 1461 patients enrolled. It found that mortality of 15% (107/730 in the artesunate group was significantly lower than the 22% (164/731) in the quinine group; an absolute risk reduction of 7%. Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (RR: 3.2; 95% CI: 1.3–7.8; *P* = 0.009). The results of this and smaller trials are consistent and suggest that artesunate is the treatment of choice for adults with severe malaria.[1]

Reconstitution (for IV administration)

- Draw up and inject the entire contents of the sodium bicarbonate 5% ampoule (1mL) into the vial which contains the artesunate powder for reconstitution.
- Shake the vial thoroughly to dissolve (approximately 2 to 3 minutes)—a significant amount of carbon dioxide gas will be produced and a clear solution should be obtained in three minutes.
- Insert an airway needle into the vial closure to vent the gas which has been produced.
- Add 5mL of sodium chloride 0.9% to the reconstituted artesunate vial and mix thoroughly to create a 10mg per mL solution (total volume is 6mL).

IV administration

- Using multiple vials when necessary, draw up the desired dose into a suitable syringe and administer by slow IV bolus at a rate of 3 to 4 mL per minute.
- The solution should be prepared freshly for each administration and should not be stored.

Presentation and cost

Artesunate is presented as artesunic acid powder 60mg (1 vial) and sodium bicarbonate 5%, 1mL (1 amp). The cost of the injection to hospitals when sourced from Central Pharmacy is approximately $42.00 per vial.

Follow-Up

Category A Special Access Scheme (SAS) paperwork

Due to its SAS requirement and limited availability, only a small quantity of emergency stock is to be held in a few selected hospitals. Subsequent supplies will only be provided by Central Pharmacy upon presentation of a completed Category A SAS form. This form must be forwarded to Central Pharmacy (Fax no: 07 3120 8561) each time the drug is ordered. When ordering replenishment stock Central Pharmacy is required to provide the company with SAS forms as validation that the unregistered product has been issued under SAS conditions.

Also, as the Category A SAS form constitutes the legal authority for an Australian sponsor to supply the specified drug, a copy of the completed form must be forwarded to the Therapeutics Goods Administration (TGA) within 28 days.

Pharmacy records

Pharmacy departments are requested to record batch numbers and other identifiers to allow retrospective identification of stock administered on individual occasions to individual patients.

Artesunate IV should be used in preference to quinine IV, if it is immediately available. Its use (refer to Therapeutic Guidelines Antibiotic 2010, version 14) should only be continued until oral therapy is possible. When the patient is able to tolerate oral therapy, a full course of artemether + lumefantrine 20mg/120mg tablets should be given. To ensure oral therapy can be administered as soon as possible, hospitals holding emergency stock of parenteral artesunate should also hold stock of artemether + lumefantrine (Riamet®) tablets which can be ordered through Central Pharmacy via the normal process.