SEVERE MALARIA IS LIFE THREATENING

Signs and symptoms of severe malaria[3]

	Adults	Children
Sign or Symptom	5–7 days	Shorter (1–2 days)
Respiratory distress/ rapid breathing and respiratory acidosis	Common	Common
Convulsions	Common (12%)	Very common (30%)
Abnormal Posturing (decerebrate, decorticate posturing and opisthotonic rigidity)	Uncommon	Common
Prostration/obtundation	Common	Common
Coma - occurence	2–4 days	Faster (1–2 days)
Neurological sequelae after cerebral malaria	Uncommon (1%)	Common (5-30%)
Jaundice	Common	Uncommon
Hypoglycaemia	Less common	Common
Metabolic acidosis	Common	Common
Pulmonary oedema	Uncommon	Rare
Renal failure	Common	Rare
CSF opening pressure	Usually normal	Usually raised
Bleeding/clotting disturbances	Up to 10%	Rare
Invasive bacterial infection (co-infection)	Uncommon (<5%)	Common (10%)

Early diagnosis and prompt treatment will save lives

Administer antimalarial medicines to a patient with suspected severe malaria without delay.

Initiate urgent treatment steps

1. Take vital signs. Start resuscitative measures immediately if required.
2. Establish intravenous access.
3. Correct hypoglycemia.
4. Control convulsions.
5. Administer IV injectable artesunate.

Do not forget to do:

- A detailed history and carefully review referral slip if available;
- Conduct a thorough but rapid clinical examination;
- Take the necessary sample for further laboratory investigations to confirm diagnosis. Do not delay treatment.

Start treatment even as the diagnosis is being confirmed via laboratory testing or rapid diagnostic test.

PRODUCT DESCRIPTION[4]

This user guide is specifically intended to support health workers with the correct use of the new injectable artesunate product Argesun® 60mg.

Artesunate powder for injection

+

Arginine/sodium bicarbonate

- **Dose for children < 20 kg: 3.0 mg/kg**
- **Dose for children ≥ 20 kg and adults: 2.4 mg/kg**

- **Artesunate for injection 60 mg vials with arginine/ sodium bicarbonate solvent can be administered IM and IV.**

What does the drug do?

Injectable artesunate is the first line treatment recommended by WHO for severe malaria, in both children and adults. It is a fast-acting agent that kills parasites more rapidly than conventional antimalarials, in particular because it is active against all stages of the parasite cycle - killing all stages including early rings, resulting in more rapid recovery.

Why does WHO recommend injectable artesunate for severe malaria?

Clinical evidence from two large-scale, multi-centre trials in South East Asia (SEAQUAMAT)[5] and Africa (AQUAMAT)[6] showed a reduction in the risk of death using injectable artesunate compared to quinine.
If used throughout Africa, injectable artesunate could save up to an additional 195,000 lives each year[7].

The advantages of injectable artesunate versus quinine

An overwhelming body of scientific evidence supports the superiority of artesunate over quinine for the treatment of severe malaria in both adults and children across the world.

- Injectable artesunate saves more lives than quinine[7].
- Injectable artesunate is better tolerated than quinine and has fewer side effects[8].
- Injectable artesunate is easier to use than quinine and is less painful[8].

What are the benefits of the New Formulation?

- Easier preparation
- Faster to use
- Less chance of errors in dilution and reconstitution

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INJECTABLE ARTESUNATE

Can injectable artesunate be safely used during pregnancy ?

Severe malaria is especially hazardous during pregnancy, therefore full dose artesunate treatment should be administered at any stage of pregnancy without delay.

What are the side effects of artesunate?

Artemisinin and its derivatives are remarkably well tolerated. Injectable artesunate like any other medication, may cause side effects, but not everybody gets them. The main adverse reaction that has been noted is a delayed haemolysis. This reaction may be more important in patients with hyper parasitaemia and in younger children. It may be difficult to differentiate the effects of severe malaria from the side effects of the medicine. Please see product insert leaflet for more details.

Interactions:

No significant adverse interactions have been documented.

IMPORTANT

Patients should be fully assessed at the referral centres and treatment continued for severe malaria or modifed as necessary based on the findings.

Finding effective medications to treat severe malaria takes decades of research. Please use medications with care and help us prevent resistance to these life saving medicines.

Do not use injectable artesunate for uncomplicated malaria.

1 WHO, World Malaria Report 2023 - https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023
2 World Health Organization (WHO) Guidelines for Malaria (16 February 2021); https://www.who.int/fr/news/item/16-02-2021-who-launches-consolidated-guidelines-for-malaria
3 WHO, Management of Severe Malaria - A practical handbook - Third edition - April 2013 - http://www.who.int/malaria/publications/atoz/9789241548526/en/
4 MA to be updated once product has been prequalified.
5 Dondorp A. *et al.* South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group ; Artesunate versus quinine for Treatment of severe falciparum malaria: a randomised trial ; *The Lancet*, Volume 366, Issue 9487, Pages 717-725, 27 August 2005.
6 Dondorp A. *et al.* Artesunate versus quinine for Treatment of severe falciparum malaria in African Children (AQUAMAT): an open-label, randomised trial ; *The Lancet*, Volume 376, Issue 9753, Pages 1647-1657, 13 November 2010.
7 Médecins Sans Frontières. Malaria: Making the Switch (2011): https://www.msf.org/malaria-making-switch
8 White NJ *et al.* Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 309:61–66 (1983).

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NEW
QUICK AND EASY PREPARATION!

USER GUIDE

ONE-STEP ARGININE-BASED FORMULATION OF INJECTABLE ARTESUNATE FOR SEVERE MALARIA

60 mg vials

Severe malaria is a medical emergency. It can lead to rapid death. Malaria caused over 608 000 deaths in 2022, mainly in children.[1] World Health Organisation (WHO) recommends injectable artesunate for the treatment of severe malaria.[2]

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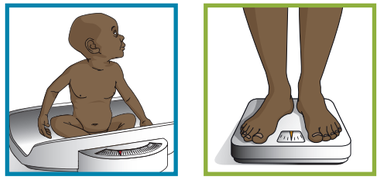
WHO RECOMMENDED

This user guide is specifically intended to support health workers with the correct use of the new injectable artesunate product Argesun® 60mg.

ARGININE-BASED FORMULATION OF INJECTABLE ARTESUNATE

1 WEIGH THE PATIENT

Carefully follow the following 5 Steps from preparation to administration.



The person prescribing artesunate must calculate the dose using the patient's weight. The administering nurse or doctor must check the calculation to confirm that it is correct.

2 CHECK NUMBER OF VIALS NEEDED AND AMPOULES OF SOLVENT NEEDED

	Number of vials (60 mg)	Number of ampoules needed
Less than 25 kg	1 vial	1 ampoule
26-50 kg	2 vials	2 ampoules
51-75 kg	3 vials	3 ampoules
76-100 kg	4 vials	4 ampoules

Use a portion of a vial or a whole vial depending on the weight of your patient. Expect some wastage, since any unused solution must be discarded, unless used for another patient within an hour.

Calculation

Less than 20 kg

Target dose: **3.0 mg per kg** of body weight

Vials of artesunate needed: $\frac{\textbf{3.0 mg} \times \text{body weight (kg)}}{\text{Product strength (60 mg)}}$

20 kg and more

Target dose: **2.4 mg per kg** of body weight

Vials of artesunate needed: $\frac{\textbf{2.4 mg} \times \text{body weight (kg)}}{\text{Product strength (60 mg)}}$

IMPORTANT

- Each vial requires separate reconstitution.
- Use immediately after reconstitution.

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3 RECONSTITUTE

Add 3 mls ampoule of arginine/sodium bicarbonate solvent to the artesunate powder. This activates the drug. Thereafter the drug is ready to use.

There is NO further dilution.

A Prepare the required vials and ampoules for reconstitution.

B Withdraw the full 3 mls content and inject the whole content into artesunate vial.

C Shake gently until the solution is clear.

D The solution is now ready for administration. Discard if not clear.

Artesunate powder	60 mg
Arginine/sodium bicarbonate solvent	3 ml
Total volume of reconstituted drug	**3 ml**
Artesunate 60 mg solution (with solvent)	60 mg/3ml = 20mg/ml

IMPORTANT

- SAME CONCENTRATION FOR IV AND IM.
- Follow sterile procedures for all steps.
- Use full content of arginine/sodium bicarbonate solvent vial/ampoule.
- Do not shake too vigorously.
- Discard if solution does not clear.
- No diluent is required for this formulation of artesunate for injection with arginine/sodium bicarbonate solvent.
- Do not add saline solution, dextrose or water to this formulation of artesunate for injection with arginine/sodium bicarbonate solvent.
- The drug is ready for administration after the arginine/sodium bicarbonate solvent has been added and the solution is clear.

4 CALCULATE THE DOSE

For intravenous route (IV) and intramuscular route (IM)

Less than 20 kg — 3.0 mg/kg

IV & IM concentration: 20 mg/ml

3.0 mg x body weight (kg) / IV artesunate solution concentration **20 mg/ml**

Example for 8 Kg child:

$\frac{3.0 \times 8}{20}$ = 1.2 mls

1.2 ml rounded up to **2 mls**

For patients less than 20 kg

Weight kg	Dose mg	Dose ml
0 - 7	20	1
7 - 10	30	2
11 - 13	40	2
14 - 16	50	3
17 - 20	60	3

20 kg and more — 2.4 mg/kg

IV & IM concentration: 20 mg/ml

2.4 mg x body weight (kg) / IV artesunate solution concentration **20 mg/ml**

Example for 26 Kg child:

$\frac{2.4 \times 26}{20}$ = 3.12 mls

3.12 ml rounded up to **4 mls**

For patients of 20 kg and more

Weight kg	Dose mg	Dose ml
20 - 25	60	3
26 - 29	70	4
30 - 33	80	4
34 - 37	90	5
38 - 41	100	5
42 - 45	110	6
46 - 50	120	6
51 - 54	130	7
55 - 58	140	7
59 - 62	150	8
63 - 66	160	8
67 - 70	170	9
71 - 75	180	9
76 - 79	190	10
80 - 83	200	10
84 - 87	210	11
88 - 91	220	11
92 - 95	230	12
96 - 100	240	12

Rounding up: to ensure an effective therapeutic dose, it is recommended to round up to the next whole number for any dose above a whole number.

What if a syringe with 0.10 decimals measurement is available? Should the dose be rounded up?

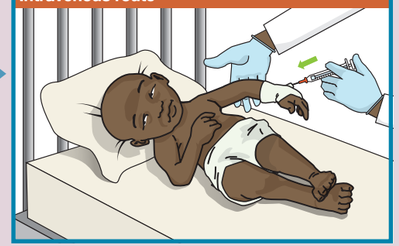
If your hospital uses syringe with 0.10 decimals allowing to withdraw the precise dose, then administer the exact dose.

5 ADMINISTER

mls	1-4 mls	4-8 mls	8-12 mls
minutes to push	1 minute	2 minutes	3 minutes

Withdraw the required dose (ml) from the prepared vial(s) :

Intravenous route

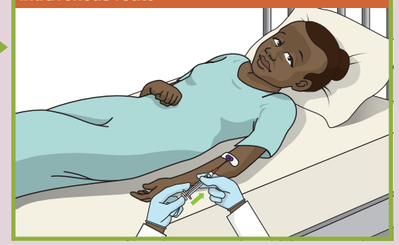


Slow injection 3-4 mls per minute.

Intramuscular route

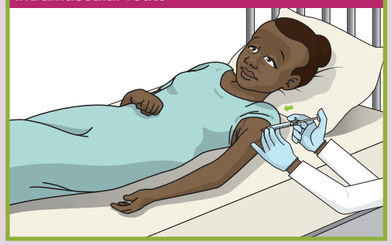
Inject in an appropriate IM site. Use multiple sites if needed. Not more than 3 mls per site.

Intravenous route



Slow injection 3-4 mls per minute.

Intramuscular route



Inject in an appropriate IM site. Use multiple sites if needed. Not more than 5 mls per site.

IMPORTANT

- Follow sterile procedures for all steps.
- Double check dose required (mls) for patient's weight (kg) before injecting.
- Each vial requires separate reconstitution.
- Use full content of arginine/sodium bicarbonate solvent ampoule.
- Do not shake too vigorously.
- Discard if solution does not clear.
- Inject immediately after preparation
- Ensure the intravenous line is patent by flushing the line **before and after** administration.
- Discard any solution not used within 1 hour.
- Prepare a fresh solution for each administration, except if the already prepared solution is used for another patient within 1hour of preparation.

This user guide is specifically intended to support health workers with the correct use of the new injectable artesunate product Argesun® 60mg.

Can injectable artesunate be used safely during pregnancy?

Severe malaria is especially hazardous during pregnancy, therefore full dose of parenteral artesunate treatment should be administered at any stage of pregnancy without delay.

DOSING SCHEDULE

Give a minimum of 3 mandatory intravenous doses over 24 hours as indicated below:

Day	Dose	Hour
Day 1	Dose 1	**0 hours** - On admission
	Dose 2	**12 hours after Dose 1**
Day 2	Dose 3	**24 hours after Dose 1**

Patient able to swallow ACT oral medication?

YES

Give oral antimalarial (ACT) for 3 days **8-12 hours after the last injectable artesunate dose.**

NO

Continue dosing every 24 hours / once per day, (**for a maximum of 7 days**) until the patient is able to take oral ACT medication.

Give oral antimalarial (ACT) for 3 days **8-12 hours after the last injectable artesunate dose.**

* Oral ACT – what are they and what are they used for?

Artemisinin-based combination therapy or ACT are combination drugs used to treat uncomplicated *P. falciparum* malaria or to complete the treatment of severe malaria after administration of injectable artesunate.

Children and adults should be treated with one of the following ACTs:

- artemether-lumefantrine (AL)
- artesunate-amodiaquine (ASAQ)
- artesunate-mefloquine (ASMQ)
- artesunate+sulfadoxine-pyrimethamine (AS+SP)
- dihydroartemisinin-piperaquine (DHA-PQP)
- artesunate-pyronaridine (PA)

Refer to the recommended ACTs in the National treatment Guidelines.

These are combination drugs because they combine artemisinin derivatives with compounds that are eliminated more slowly.

IMPORTANT

Injectable artesunate must always be followed by a 3-day course with an ACT. This is to ensure a complete treatment and to mitigate the risk of resistance development. Injectable artesunate must not be used for uncomplicated malaria.

Note: This document is intended to demonstrate to health workers how to prepare and administer the novel injectable artesunate, a treatment for severe malaria. It is not intended to provide personal medical advice. The responsibility for the interpretation and use of this material lies with the reader. In no event shall MMV be liable for damages arising from its use.