Global **Malaria** Programme

Rectal artesunate for pre-referral treatment of severe malaria

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INFORMATION NOTE

BACKGROUND

Severe malaria is a medical emergency: mortality from untreated severe malaria (particularly cerebral malaria) approaches 100%. With prompt, effective antimalarial treatment and supportive care, however, this rate falls to 10–20% overall. In areas, where comprehensive treatment and care cannot be provided, a number of pre-referral treatment options could be used, depending on the age of the patient and the availability of medicines. Rectal artesunate is one of these options: it is recommended for pre-referral treatment of severe malaria in children under 6 years of age in remote areas, so that cases of suspected malaria, e.g. at community level, can be treated without delay, pending immediate transfer to a higher-level facility where comprehensive care can be given.

Despite their highly beneficial role, rectal formulations of artemisinin derivatives are often misused in malaria-endemic countries. Especially in the private sector, rectal artesunate is used at suboptimal doses to treat uncomplicated malaria, which induces sub-therapeutic blood levels and thus increases the risks for the development and spread of resistance to artemisinins.[1]

Particularly in African countries, the rate of mortality from severe malaria remains unacceptably high. Access to treatment is still poor in many areas, and the rational use of rectal artesunate is key to reducing mortality due to severe malaria and at the same time to preserving artemisinins from the risk that resistance to them will develop. This would have devastating consequences on people's health in malaria-endemic countries and could reverse the progress in malaria control achieved in many countries over the past decade. No alternative medicines are ready to enter the market in the next few years that could replace artemisinin-based combination therapies (ACTs), the mainstay of treatment for malaria.

World Health Organization

WHO/HTM/GMP/2017.19

The first rectal artesunate product was approved for time-limited procurement under the Global Fund Expert Review Panel mechanism in December 2016. The recommendations of the Global Fund for procurement are updated regularly and compiled in the Global Fund List of Malaria Pharmaceutical Products, which is accessible from: https://www.theglobalfund.org/media/4756/psm_productsmalaria_list_en.pdf. Because of efforts by pharmaceutical manufacturers to meet WHO-prequalification requirements, it is expected that quality-assured rectal products will soon become commercially available for large-scale public sector procurement.[2]

This information note is based on current WHO recommendations. Its aim is to prepare countries for large-scale deployment of rectal artesunate for pre-referral treatment of severe malaria in children.

SEVERE FALCIPARUM MALARIA – SIGNS AND SYMPTOMS

Severe malaria manifests with a number of signs and symptoms, which can occur singly or, more commonly, in combination in the same patient (see Box 1).

BOX 1.
Clinical features of severe malaria[3]

- impaired consciousness (including unrousable coma);
- prostration, i.e. generalized weakness so that the patient is unable to sit, stand or walk without assistance;
- multiple convulsions: more than two episodes within 24 h;
- deep breathing and respiratory distress (acidotic breathing);
- acute pulmonary oedema and acute respiratory distress syndrome;
- circulatory collapse or shock, systolic blood pressure < 80 mm Hg in adults and < 50 mm Hg in children;
- acute kidney injury;
- clinical jaundice plus evidence of other vital organ dysfunction; and
- abnormal bleeding.

The risk of children for death from severe malaria is greatest in the first 24 h. The interval between the appearance of the first signs of severe illness and reaching a health facility where the appropriate parenteral treatment can be administered is usually long in most malaria-endemic countries. As the progression of severe malaria from severe illness to death can be very rapid, prompt access to pre-referral treatment can save lives.

WHO RECOMMENDATION

In order to reduce mortality, particularly in remote areas, it is recommended that patients receive pre-referral treatment. The choice of treatment should take into consideration the age of the patient and the availability of medicines (Box 2). Regardless of which pre-referral treatment is chosen, it is essential that the patient be referred immediately to a facility where the required comprehensive treatment for severe malaria (which includes parenteral and oral medicines, see Box 3) can be provided to cure the patient. The flow chart illustrates the various pre-referral and treatment options for severe malaria.

BOX 2.
WHO recommendations for pre-referral treatment of severe malaria[4]

Pre-referral treatment options for adults and older children

- In cases of suspected severe malaria in which complete treatment of severe malaria is not possible but injections are available, both adults and children should be given a single intramuscular (i.m.) dose of artesunate and be referred immediately to an appropriate facility for further care.
- Where i.m. artesunate is not available, use i.m. artemether or, if that is not available, use i.m. quinine.

Pre-referral rectal artesunate for children under 6 years of age

- In cases of suspected severe malaria in which complete treatment of severe malaria is not possible but injections are available, children under 6 years of age should be given a single intramuscular (i.m.) dose of artesunate and be referred immediately to an appropriate facility for further care.
- Where i.m. artesunate is not available, children under 6 years of age should be treated with a single rectal dose (10 mg/kg body weight) of artesunate and be referred immediately to an appropriate facility for further care.
- The recommended pre-referral treatment options, in descending order of preference (most preferred > least preferred) are:
  i.m. artesunate > rectal artesunate > i.m. artemether > i.m. quinine
- Rectal artesunate should not be used in older children or adults.

BOX 3.
WHO recommendation for treatment of severe malaria

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with i.v. or i.m. artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT (add single-dose primaquine in areas of low transmission).

FLOW CHART

Pre-referral treatment and immediate referral for comprehensive treatment of severe malaria

Pre-referral treatment options and treament of severe malaria

Immediate action and **comprehensive** treatment and care is required to prevent death, obtain cure and prevent resistance

Pre-referral treatment options for severe malaria depending on age of patient and availability of medicines

Children and adults

- ☐ Single dose of i.m. artesunate
  - – Order of preference: Where i.m. artesunate is not available, use i.m. artemether or, if that is not available, use i.m. quinine.

Children under 6 years

- ☐ Single dose of i.m. artesunate
- ☐ In areas where i.m. artesunate is not available: Single rectal dose of artesunate
  - – Rectal artesunate should not be used in older children and adults.
  - – Order of preference: Where i.m. artesunate is not available, use rectal artesunate. If neither injectable nor rectal artesunate is available, use i.m. artemether or, if that is not available, use i.m. quinine.

Immediate referral to a facility where comprehensive treatment can be provided

Treatment of severe malaria for both children and adults

Children and adults

- ☐ **Step 1. Injectable artesunate** (for at least 24 h)
- ☐ **Step 2. ACT** (full 3-day course once patient tolerates oral treatment)

CONSIDERATIONS FOR THE IMPLEMENTATION AND CORRECT USE OF RECTAL ARTESUNATE

Narrow window of indication

- When i.m. injections can be given, i.m. artesunate should be given as the pre-referral treatment of choice to both adults and children (Box 2).
- When i.m. artesunate is not available, rectal artesunate should be given to children under 6 years of age with suspected severe malaria, as they are usually unable to tolerate oral medication.
- Rectal artesunate should be administered to children under 6 years of age with suspected severe malaria in areas where the referral time is expected to exceed 6 h, such as remote rural areas.
- Use of rectal artesunate as pre-referral treatment of severe malaria in older children and adults has been associated with increased mortality; for this reason, WHO recommends this intervention only for children under 6 years of age.
- Rectal artesunate – as well as injectable formulations – should be used for severe malaria only; neither should be used for the treatment of uncomplicated malaria.

Intra-rectal administration, immediate referral and completion of full treatment

- A single dose of 10 mg/kg body weight of artesunate should be given as a suppository rectally as soon as a presumptive diagnosis of severe malaria has been made.
- For community health workers and in places with limited diagnostic capacity for severe malaria, the WHO algorithm for giving rectal artesunate for pre-referral treatment of severe febrile illness in children under 5 years described below should be followed.[5]

☐ **if fever AND** ☐ Convulsions or ☐ Unusually sleepy or unconscious or ☐ Not able to drink or feed anything or ☐ Vomits everything	☐ **Give rectal artesunate suppository (100 mg)** ☐ Age 2 months up to 3 years 1 suppository ☐ Age 3 years up to 5 years 2 suppositories

- As severe malaria is a life-threatening medical emergency, children should rather be over- than under-dosed, so that children weighing up to 10 kg should receive one suppository of 100 mg artesunate, and children weighing up to 20 kg should receive two 100 mg suppositories.

- To administer the medicine, remove the suppository from the wrapper and insert it rectally; then, cover the buttocks of the child for 1–2 min. If the suppository slips out and is still intact, reinsert the same one. If it bursts or has partially melted, insert a new suppository.

- If the suppository is expelled from the rectum within 30 min of insertion, insert a new suppository and hold the buttocks together for 10 min to ensure retention of the dose.

- It is crucial that, after administration of rectal artesunate, the child be immediately transported to a higher-level facility where i.m. or intravenous artesunate can be given for at least 24 h and adequate management of severe malaria is available. Once a child can take oral medication, he or she should receive a full 3-day treatment course with an appropriate ACT to ensure complete cure of the infection.

- If referral is impossible, rectal treatment could be continued until the patient can tolerate oral medication. As soon as the child can tolerate oral medication, he or she should receive a full 3-day treatment course of an appropriate ACT to ensure complete cure.

**WellSense developed & field tested these materials & designed & coordinated a study in Malawi to measure the value of these materials in practice.

For more details, see the Medicines for Malaria Venture tool kit on rectal artesunate (https://www.mmv.org/access/tool-kits/rectal-artesunate-tool-kit), which also provides job aids and guides for community health worker training in English, French and Portuguese. Pre-referral rectal artesunate treatment of childhood malaria in the community – training manual for community health workers to assess danger signs, provide emergency pre-referral treatment and refer treated children to a health facility can be accessed on the TDR web page at: http://www.who.int/tdr/publications/rectal_artesunate/en/.

Product quality

- Only rectal artesunate formulations of proven quality should be used. Recently, the Global Fund included 100 mg rectal artesunate suppositories on the list of products reviewed by its Expert Review Panel for time-limited procurement from one quality-assured manufacturer. The full list of quality-assessed products (including ACTs) is accessible at: https://www.theglobalfund.org/media/4756/psm_productsmalaria_list_en.pdf.[6]

Quality of care and monitoring

- **Improving access to care in line with WHO recommendations.** To ensure the life-saving benefits of rectal artesunate and to avoid its misuse as monotherapy, correct use should be promoted and closely monitored. Programmes should include a structured supervision and mentoring system at multiple levels of the health care system in which artesunate suppositories are available (including the private sector and communities) and periodic assessment of the quality of care.[7] Supervision should include on-site mentoring, so that any deviation from practice can immediately be corrected.

In all places in which rectal artesunate will be used, the referral systems and capacity for management of severe malaria of referral sites should be strengthened, where applicable, to ensure the availability of the required commodities (injectable artesunate, effective ACT) for the continuum of care from community level to referral facility.

- **Resistance.** Molecular markers have been identified for artemisinin resistance: specific mutations in the *Kelch 13* (K13)-propeller domain are associated with delayed parasite clearance in vivo and in vitro. Surveillance of artemisinin resistance in line with WHO recommendations should be implemented in areas and countries where rectal and injectable artesunate are being used.

- **Mortality.** Countries should closely monitor the effect of use of rectal artesunate as pre-referral treatment on the case fatality rate due to severe malaria at referral facilities where treatment is completed with injectable formulations, stratified by age group.

Box 4 summarizes the main points for rational use of rectal artesunate in the form of a checklist.

BOX 4.
Summary checklist for the use of rectal artesunate as pre-referral treatment of severe malaria

- ☐ Use only in children **under 6 years** of age with **suspected** severe malaria or severe febrile illness, if i.m. artesunate is not available.
- ☐ After administration of rectal artesunate, **immediately refer** the patient to a higher level of the health care system where comprehensive care for severe malaria can be provided.
- ☐ Confirm the diagnosis of severe malaria, and provide **full treatment with injectable antimalarials for at least 24 h**, followed by a **complete 3-day treatment course** with an effective **ACT** as soon as the patient can tolerate oral medication. Add a single low dose of primaquine (except in infants under 6 months of age) in areas of low transmission.
- ☐ **Do not** use rectal artesunate (or injectable artesunate) without completing the full required treatment cycle as described above.
- ☐ Use only rectal artesunate procured from **quality-assured** sources.
- ☐ **Ensure quality of care and monitoring:**
  - ☐ Improve access to rectal artesunate, in line with WHO recommendations.
  - ☐ Monitor resistance.
  - ☐ Monitor case fatality of severe malaria at referral level.
- ☐ **Never** use rectal artesunate to treat uncomplicated malaria.

Endnotes

1. In April 2017, the WHO Global Malaria Programme published the latest status report on artemisinin resistance (http://www.who.int/malaria/publications/atoz/artemisinin-resistance-april2017/en/). Foci of artemisinin resistance have been identified in the South-East Asia and South America.

2. Currently, two pharmaceutical manufacturers have submitted their product dossiers for review to the WHO Prequalification Programme. The latest list of WHO prequalified products is accessible at: https://extranet.who.int/prequal/content/prequalified-lists/medicines.

3. Management of severe malaria – A practical handbook, 3rd edition. Geneva: World Health Organization; 2017 (http://apps.who.int/medicinedocs/documents/s20170en/s20170en.pdf).

4. Guidelines for the treatment of malaria, 3rd edition. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/9789241549127/en/).

5. Caring for newborns and children in the community: a training guide for community health workers. Geneva: World Health organization; 2011 (http://apps.who.int/iris/bitstream/10665/44398/1/9789241548045_Manual_eng.pdf).

6. Once rectal artesunate attains WHO pre-qualified status, information on sources will be available on the web page of the WHO Prequalification Programme: http://apps.who.int/prequal/.

7. Cardemil CV, Gilroy KE, Callaghan-Koru JA, Nsona H, Bryce J. Comparison of methods for assessing quality of care for community case management of sick children: an application with community health workers in Malawi. Am J Trop Med Hyg 2012;87(Suppl 5):127–36.