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artesunate

The standard intravenous treatment for severe attacks of malaria

● **Intravenous *artesunate* is more effective in reducing mortality than injectable *quinine*. It also has a better adverse effect profile and is more convenient to use.**

A REAL ADVANCE

Plasmodium falciparum malaria can be life-threatening, particularly in young children, migrants, travellers and pregnant women (1). Brain damage with encephalopathy and coma due to severe malaria is fatal in about 20% of cases (about 50% during pregnancy). More than 2% of survivors have neurological sequelae (1). Severe anaemia is another potentially life-threatening complication.

Intravenous *artesunate* (Malacef°, marketing authorisation holder Guilin Pharma) is the standard treatment for severe malaria (1-4). Two large randomised controlled trials including thousands of adults and children have shown that it is more effective in reducing mortality than injectable *quinine*: the respective mortality rates were 15% and 22% in a trial in South-East Asia, and 10% and 12% in a trial in Africa (1-4).

In France, despite a decline in the number of cases of imported malaria, about 100 to 200 cases of severe malaria are reported each year, resulting in 10 to 20 deaths (4). In addition, *P. falciparum* malaria is endemic to Mayotte and Guyana, two French overseas territories.

In May 2011, IV *artesunate* was granted temporary authorisation for use in hospitals according to a protocol defining treatment modalities and data collection (5,6). How effective is IV *artesunate*, particularly in non-endemic areas?

Case series in non-endemic areas. Evaluation of IV *artesunate* in the treatment of severe malaria in non-endemic areas is mainly based on eight case series (five in Europe and three in the United States) involving a total of 310 patients treated between 2008 and 2013 (4). The largest series (a third of all cases) included patients treated in France between May 2011 and November 2012, following temporary authorisation.

Overall mortality was 4.8%. The mortality rates reported in two French studies of imported malaria treated with IV *quinine* were 10.5% between 2000 and 2006 and 5.2% between 2007 and 2010, but it should be noted that indirect comparisons of this type provide only weak evidence (4).

In France, 113 patients with a mean age of 41 years were treated with IV *artesunate* for severe malaria, starting about 4 days after symptom onset, within the framework of the temporary authorisation protocol; *artesunate* was the only antimalarial treatment in 66 cases (6). Clinical outcome was favourable in 107 cases. Six patients (5.3%) died of multiorgan failure.

Delayed haemolytic anaemia? The adverse effects of artemisinin derivatives, such as *artesunate,* mainly consist of gastrointestinal, cutaneous and neurological disorders, as well as neutropenia, liver enzyme elevations, and QT prolongation (1-5).

In addition, 19 patients in Europe and Japan developed haemolytic anaemia between one week and one month after the end of IV *artesunate* therapy (7). Twelve patients required blood transfusions following treatment with IV *artesunate*. The anaemia resolved within four to eight weeks. As a link with *artesunate* is suspected, haematological follow-up is warranted up to four weeks after the beginning of treatment (4,6,7).

Hypoglycaemia is less frequent with IV *artesunate* than with injectable *quinine* (1-4).

Pregnancy. In France, IV *artesunate* was used to treat four pregnant women within the context of the temporary authorisation protocol (4). One spontaneous miscarriage occurred following administration in early pregnancy, but malaria can also cause spontaneous abortion, stillbirth and prematurity (4).

Despite the toxicity of artemisinin derivatives to the human embryo, the benefits of IV *artesunate* outweigh the risk of death from severe malaria during pregnancy (4).

artesunate powder and solvent for solution for IV injection

MALACEF°

• **60 mg** of *artesunate* per vial (solvent: one 1-ml ampoule of 5% *sodium bicarbonate*)

antimalarial

■ **Indications:** *"(...) treatment of severe attacks of Plasmodium falciparum malaria".* [French temporary authorisation for use on a named patient basis according to a fixed protocol; national procedure]

More convenient than quinine. Intravenous *artesunate* injection takes minutes, while *quinine* is infused over 4 hours and requires cardiac monitoring.

To avoid late resurgence of parasitaemia, IV treatment is followed by oral combination therapy using an artemisinin derivative (in France, *artemether* + *lumefantrine*) (5,8).

In practice. Intravenous *artesunate* is the treatment of choice for severe attacks of *Plasmodium falciparum* malaria. Full marketing authorisation in the EU would improve access to this drug.

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Selected references from Prescrire's literature search

In response to our request for information, Guilin Pharma provided us with administrative documents and published articles, as well as packaging items.

1- Prescrire Editorial Staff "Artemisinin derivatives and malaria. Useful, in combination with other antimalarials" *Prescrire Int* 2008; **17** (96): 162-168.
2- Prescrire Editorial Staff "Severe malaria: artesunate is now the standard treatment" *Prescrire Int* 2011; **20** (120): 245.
3- World Health Organization "Guidelines for the treatment of malaria" 2nd ed. 2010: 216 pages.
4- Haut conseil de la santé publique "Place de l'artésunate injectable dans le traitement du paludisme grave de l'adulte et de l'enfant" 1 February 2013: 46 pages.
5- ANSM "Protocole d'utilisation thérapeutique et de recueil d'informations - Malacef (artésunate) 60 mg, poudre et solvant pour solution injectable" April 2013: 42 pages.
6- ANSM "Résumé du rapport de synthèse n° 3 - Malacef (artésunate) 60 mg, poudre et solvant pour solution injectable" April 2013: 5 pages.
7- Centers for Disease Control and Prevention "Published reports of delayed hemolytic anemia after treatment with artesunate for severe malaria - worldwide, 2010-2012" *MMWR* 2013; **62** (1): 5-8.
8- Prescrire Rédaction "Comparer pour décider. Traitement de l'accès de paludisme non compliqué à Plasmodium falciparum" *Rev Prescrire* 2013; **33** (360): 732-733.

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