

BLOFAST

Artesunate + Mefloquin Tablets for Adults

Composition: Each kit contains individual tablets of

(A) Artesunate Tablets (3 Tablets)

Artesunate	200mg
Excipients	q.s

(B) Mefloquin Tablets (3 Tablets) each tablet contains

Mefloquin Tablets Hydrochloride BP	275mg
e.g. to Mefloquin base	250mg
Excipients	q.s

Properties/Effects

Blofast is a free combination of two anti-malarial drugs, artesunate and mefloquin. Artesunate is a water-soluble hemisuccinate ester of artemisinin; the main anti-malarial substance isolated from *Artemisia annua* and mefloquine is an anti-malarial agent of the 4-quinoline methanol group. Both active ingredients are schizonticidal and destroy the erythrocytic asexual forms of the causative agents of malaria in humans (*plasmodium falciparum*, *plasmodium ovale*). Blofast is usually also effective against malaria pathogens that have developed resistance to either agent used alone and to other anti-malarial agents such as chloroquine, proguanil, pyrimethamine as well as pyrimethamine-sulfadoxine combinations.

A three-day treatment course with a combination of artesunate and mefloquine was shown to induce faster symptomatic response with shorter parasite clearance times than mefloquine alone, and less recrudescence as compared to artesunate mono-therapy when used for less than 5 days.

In a randomized, double blind, parallel group, comparative, multicenter study in 104 African Patients with uncomplicated *P. falciparum* malaria, Blofast showed a 100% cure rate at day 14 with no recrudescence by day 28, and mean fever and parasite clearance times of 32 and 45 hours respectively.

Pharmacokinetics

Pharmacokinetics characteristics of the artesunate and mefloquin combination have been investigated in various clinical studies. There was no evidence of a clinically significant interaction between the two anti-malarial agents.

Absorption

Artesunate

Following oral administration, artesunate is quickly absorbed and reaches a maximum plasma concentration (C_{max}) on average between 0.5 and 1 hour

Mefloquin

Following single oral administration of mefloquine, a maximum plasma concentration is reached within 6 to 24 hours (mean 17 hours). At a dose of 1000mg of mefloquin, plasma concentrations (C_{max}) of approximately 1000 pg/l can be measured. The presence of food in stomach increases the rate and extent of absorption and leads to an increase in bioavailability of approximately 40%.

Distribution

Artesunate

The concentration of DHA (dihydroartemisin, the bioactive metabolite of artesunate) in *P. falciparum*-infected erythrocytes in vitro was found to be 300-fold the plasma concentration (compared to less than 2-fold for uninfected erythrocytes). Artesunate and DHA bind modestly to human plasma protein. The degree was found to be about 59% for artesunate and 43% for DHA.

Mefloquin

Depending on the parasithemic state and the duration of the infection, the concentration of mefloquin in erythrocytes is almost two to four times that of the plasma concentration. The volume of distribution is between 16 and 251/kg. More than 98% of the active ingredient is bound to plasma proteins. Mefloquine crosses the placental barrier and reaches breast milk in apparently minimal amounts.

Metabolism

Artesunate

In vivo, artesunate is hydrolysed rapidly probably by blood esterases and the hepatic cytochrome P450 system, to dihydroartemisinin (DHA), which is also highly effective against malaria.

Mefloquine

Several metabolites of mefloquine have been identified. The major metabolite is the corresponding quinoline carboxylic acid, which is inactive against *P. falciparum*.

Elimination

Artesunate

The mean elimination half-life of artesunate is approximately 0.5 hours. The active metabolite dihydroartemisinin (DHA) has a mean elimination half-life of 0.75 hours and is eliminated slower than the parent compound. DHA is cleared predominantly by hepatic biotransformation to pharmacological inactive metabolites.

Mefloquine

The mean elimination half-life of mefloquine is 21 days (15-33 days). Total clearance, which is essentially hepatic, is approximately 30ml/min. There is evidence that mefloquine is eliminated mainly via bile and faeces. In volunteers, elimination of unchanged mefloquine and its major metabolite in urine was 9% and 4%, respectively, of the administered dose. It was not possible to determine the concentrations of other metabolites in the urine.

Kinetics in special clinical situations

There have been no specific pharmacokinetic studies for mefloquine and artesunate in patients suffering from renal insufficiency, however, only a small fraction of these active substances is eliminated via the kidneys. It should be noted that mefloquine and its principal metabolite are not removed to an appreciable extent by haemodialysis. Accordingly, no dose adjustment is necessary for Blofast in patients with impaired renal function. It has been shown that hepatic insufficiency has no effect on the bioavailability and clearance of oral artemisinin. However, no specific data is available on the use of artesunate in this patient population. In addition, the elimination of mefloquine in such patients may be delayed, which leads to higher plasma concentrations. Therefore caution is advised in patients with hepatic insufficiency receiving Blofast. The pharmacokinetic difference regarding mefloquine has been observed between various ethnic populations. In practice however, host and the sensitivity of the parasite.

Indications/Possibilities for use

Blofast is indicated for the oral treatment of non-complicated *P. falciparum* malaria in high transmission endemic areas (e.g Africa). It can also be used for treating multi drug resistant strains of *P. falciparum*, as well as malaria caused by mixed Plasmodium pathogens.

Dosage/Use

Partially immune adults and children with a body weight between 30 and 55kg. A treatment course comprises 3 daily doses of two tablets i.e. one artesunate 200mg tablet and one mefloquine 250mg tablet given simultaneously, once daily for 3 consecutive days. The dose of two tablets is given at the time of initial diagnosis, followed by a second dose of 2 tablets 48 hours thereafter the initial dose. If Blofast daily dose (2 tablets) is missed, the patient should be advised to take the missed dose (2 tablets) as soon as it is realized that it has been forgotten. The next dose (2 tablets) should be taken after a further 24 hour interval. Patients who vomit within less than 30 minutes after administration of any Blofast daily dose (2 tablets) should be a replacement (full) dose of 2 tablets. In this case the prescription of another Blofast pack should be considered. Parts of this new pack may be used to ensure that the patient will complete a 3-day full treatment course with Blofast. Following treatment with Blofast of malaria caused by a mixed infection with *P. vivax*, relapse prophylaxis with an 8-amino quinoline derivate (e.g. primaquine) should be considered to eliminate hepatic forms of the parasite. Non-immune patients and patients with a body weight of more than 55kg for these patients, higher Blofast doses might be more appropriate. Children with less than 30kg body weight. Due to limited clinical experience, Blofast is currently not recommended for use in patients who have less than 30kg body weight. Different Blofast dosage regimens are still under evaluation in children.

Mode of Administration

The 2 tablets constituting a Blofast daily dose must be taken simultaneously without chewing them, with a large amount of liquid and if possible with a meal. For patients having difficulties with swallowing the tablets can be crushed and dissolved in some water.

Restriction On Use

Contraindication

Blofast is contraindicated in patients with a known hypersensitivity to artesunate or mefloquine, to their chemically related compounds like other artemisinin derivatives, quinine or quinidine, or to any other ingredient of the tablets.

Precautions

Blofast is not recommended for the prophylaxis of malaria in epileptics, mefloquine may increase the risk of seizures. In these patients, Blofast should therefore only be used if absolutely required by the medical condition.

Halofantrine, which is known to cause QT interval prolongation, must not be administered concomitantly with or after a mefloquine containing antimalarial agent like Blofast, because of risk of a potentially fatal prolongation of the QT interval.

Incidents of dizziness, disturbed sense of balance or neuropsychiatric reactions have been reported both during use and up to three weeks after the last dose of mefloquine due to its long half-life. Therefore, caution is also advised in patients receiving Blofast when driving vehicles, piloting aircrafts, operating machinery, deep sea diving or pursuing other activities requiring full attention and fine-motor coordination.

Due to limited clinical experience, Blofast is currently not recommended for use in patients who have less than 30kg body weight.

Pregnancy/Lactation

Pregnancy category C

As experienced in pregnant patients is limited, Blofast should not be administered during pregnancy unless the treatment is considered life saving and the expected benefit justifies the potential risk for the foetus. Likewise, women of childbearing age should use contraceptive measures for up to three months after treatment with Blofast.

Clinical experience with artesunate or mefloquine used as monotherapy has not revealed any embryo toxic or teratogenic effects. Mefloquine passes in small quantities into breast milk, the effects have been observed in breastfed infants whose mothers took mefloquine.

Undesirable effect

Adverse events experienced by patients taking anti-malarial drugs often mirror the symptoms of an acute malaria infection. It may therefore not be possible to distinguish undesirable effects of Blofast from the symptoms of the disease.

The most common adverse experiences reported in clinical studies on patients treated with Blofast.

Gastrointestinal disorders

Common abdominal pain, nausea, vomiting and diarrhea, nervous systems disorders, very common dizziness, common insomnia, general disorders, common asthenia, anorexia. Common 1 to 10% very common, 10% or more. Most of these adverse events were of mild to moderate severity and occurred with a similar frequency, when historically compared to the incidence rate of adverse events observed in patients receiving either drug as monotherapy. No other significant adverse effects have been observed in patients

treatment with Blofast nevertheless, any other side effects that have been reported with either artesunate or mefloquine used as mono-therapy could also occur with Blofast.

In addition, the following most common adverse events have been reported in the literature with the combination of artesunate and mefloquine; headache and allergic reactions including rash and pruritus. In rare cases mild and transient reduction in reticulocytes and neutrophil granulocytes, as well as transient increase in transaminases and total bilirubin have been described.

Interactions

So far, there have been no reports of negative drug interactions with artesunate. Concomitant administration of mefloquine and related substances (e.g. quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and increase the risk of convulsions. Therefore, halofantrine, which is known to cause QT interval prolongation, must not be administered concomitantly with or after Blofast for at least weeks. In patients undergoing treatment with anticonvulsive such as valproic acid, carbamazepine, Phenobarbital or phenytoin, mefloquine contained in Blofast may lower the plasma concentration of the anticonvulsive, resulting in seizures. In such cases, it may be required to adjust the dosage of the anticonvulsive (See Restrictions on use)

Over Dosage

So far, no causes of overdose have been reported with artesunate. Over dosage with mefloquine may lead to increased occurrence of the mefloquine-related adverse effects. Recommended therapy in case of Blofast over-dosage consists of vomiting or gastric lavage and careful monitoring of the cardiac function (if possible by ECG) and of neuropsychiatric status (for at least 24 hours)

Storage

Store in cool, dry & dark place.

KEEP MEDICINES OUT OF REACH OF CHILDREN

Presentations: A blister pack contains

3 Tablets of Artesunate 200mg + 3 Tablets of mefloquine 250mg

The Tablets are organized in the pack in such a way that it can easily be seen on the Aluminium foil which tablets to take on which way