PACKAGE LEAFLET: INFORMATION FOR THE USER

Malacef® 60, 60 mg artesunate
powder and solvent for solution for injection

This medicine is used for treatment by hospital physicians only. This medicine is provided on pharmacy-to-pharmacy-delivery basis. Artesunate has an Orphan Drug Designation (EU/3/07/430).

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT MALACEF 60 IS AND WHAT IT IS USED FOR
Malacef 60 contains artesunate. Artesunate is a soluble artemisinin derivative indicated for the emergency treatment of severe and/or complicated malaria caused by *P. falciparum* and *P. vivax*.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE MALACEF 60

Do not use Malacef 60
If you are allergic to artesunate, other artemisinin-derivatives or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Severe Falciparum malaria infections usually require additional therapy, like infusions and paracetamol. When the critical phase of the Falciparum malaria infection has passed, it is advised to weekly check your blood for parasites. If reinfection or recrudescence occurs, you should be treated with another antimalarial drug. Other antimalarials are also necessary when a mixed infection with *P. vivax* has been established or is suspected.

In a clinical observational study with Malacef 60 late-onset haemolytic anaemia and persistent haemolytic anaemia have been seen (see also section 3 “what to do after treatment with artesunate”).

There are no adjustments in dosing necessary if you have a decreased renal or hepatic function.

Children
The safety and efficacy for children has been proved in a large clinical trial (AQUAMAT).

Other medicines and Malacef 60
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This particularly applies if you use one of the following medicines: chloroquine and chloroquine-derivatives, omeprazole, free radical scavengers (like ascorbic acid and vitamine E).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
Not enough data are available on the use of this medication during pregnancy.
Ask your doctor for advice before taking this medicine.

Breast-feeding
Limited information indicates that dihydroartemisinin, the active metabolite of artesunate is present at low levels in breast milk. It is advised to (temporarily) stop breast-feeding.

Driving and using machines
No information available.

3. HOW TO USE MALACEF 60

The dose of Malacef 60 is determined by the specialist internal medicine. Malacef 60 is administrated by intravenous injection.

The recommended dose is 2.4 mg per kg body weight at T=0, T=12, T=24 hours and subsequently every 24 hours. Switch to oral therapy as soon as possible. To minimize the chance of recrudescence it is important that you are treated with an antimalarial drug for 7 consecutive days.

Use in children
The recommended dose for children weighing 20 kg or more as for adults is: 2.4 mg per kg body weight.
The recommended dose for children weighing less than 20 kg is 3 mg per kg body weight.

How should this product be prepared?
- Add the sodium bicarbonate solution (1 ml) to the vial with the powder
- Shake until the solution is clear
- Let the gas (CO_2) escape from the vial through a needle
- Add 5 ml glucose 5% or 5 ml sodium chloride 0.9% solution to the vial
- Swirl to form a homogeneous solution
- This solution should be administered

After reconstitution 1 ml of solution contains 10 mg artesunate.
The total solution is 6 ml.
The rate of infusion should not exceed 3 ml per minute.
The solution should preferably not be added to an infusion.

What to do after treatment with artesunate
Late-onset haemolytic anaemia has occurred (see also section 2 “warnings and precautions”). Therefore it is advised to check hemoglobin weekly after treatment with artesunate for a period of 4 weeks. If there is deterioration or insufficient improvement in the blood picture or when in doubt, it is advisable to check other parameters for haemolytic anaemia (see also section 4 "Possible side effects").

If you use more Malacef 60 than you should
Contact your doctor as soon as possible.

If you forget to use Malacef 60
Do not take a double dose to make up for a forgotten dose.

If you stop using Malacef 60
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been mentioned for artesunate and artemisinin-derivatives.
Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
- Uncommon: (occasionally severe) reduction in leukocytes (neutropenia), blood disorder with symptoms like bruises and bleeding tendency (thrombocytopenia)
- Very rare: pure red cell aplasia
- Frequency not known: reversible dose-dependent reduction in reticulocytes (reticulocytopenia). In a clinical observational study with Malacef 60 late-onset haemolytic anaemia and persistent haemolytic anaemia have been seen. Both effects are reversible

Immune system disorders
- Uncommon: hypersensitivity
- Rare allergic reaction (estimated risk 1 in 3000 patients), which involved urticarial rash as well as other symptoms, including itch (pruritus), oedema, hypotension and/or dyspnoea

Nervous system disorders
- Common: dizziness, light-headednesss, headache, sleeplessness (insomnia)
- Very rare: peripheral neuropathy (or the perception of tickling, itching or tingling without any reason (paraesthesia))
- Frequency not known: convulsions

Ear and labyrinth disorders
- Common: tinnitus (with or without decrease in auditory function)

Cardiac disorders
- Frequency not known: electrocardiographic disturbances like decreased heart rate (bradycardia) and a possible non-relevant prolongation of the QT-interval

Respiratory, thoracic and mediastinal disorders
- Uncommon: coughing, nasal congestion

Gastrointestinal disorders
- Common: bitter/alterated taste, nausea, vomiting, abdominal pain or cramps, diarrhea
- Rare: raised serum amylase, inflammation of the pancreas with symptoms like severe pain in the upper abdomen radiating to the back, nausea and vomiting (pancreatitis)
- Frequency not known: flatulence, lack of appetite (anorexia)

Hepatobiliary disorders
- Uncommon: transient rises in liver values (AST, ALT)
- Rare: liver inflammation (hepatitis)
- Frequency not known: late onset pancreas inflammation (pancreatitis)

Skin and subcutaneous tissue disorders
- Uncommon: rash, hair loss (alopecia)
- Frequency not known: itch (pruritus)

Musculoskeletal and connective tissue disorders
- Uncommon: arthralgia, muscle disorders

Renal and urinary disorders
- Frequency not known: increased urine production

General disorders and administration site conditions
- Common: fatigue, discomfort, pain at injection site
- Frequency not known: drug-induced fever, bodypains

Reporting of side effects
If you notice any side effects, you should report to your doctor or pharmacist. It includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE MALACEF 60

Keep this medicine out of the sight and reach of children.

Store in original package in order to protect from light and moisture.
Do not store above 25 °C.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if the solution is not clear.

Remark: After reconstitution the solution must be used within 6 hours.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Malacef 60 contains
The active substance is artesunate.
The other ingredient is sodium bicarbonate solution for dissolving the artesunate.

What Malacef 60 looks like and contents of the pack
One carton contains one vial with 60 mg artesunate, powder for solution for injection and one ampoule with 1 ml sodium bicarbonate solution 5%.

Manufacturer, Importer and Distributor
Manufacturer: Guilin Pharmaceutical Co., Ltd., China
Importer and distributor: Ace Pharmaceuticals BV, Schepenveld 41, 3891 ZK Zeewolde, T +31 36 5474091 (Medical Information)

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