**Mefloquin 250 mg tablets**

This information is a summary only. It does not contain all information about this medicine. If you would like more information about the medicine you are taking, check with your doctor or other health care provider. No rights can be derived from the information provided in this medicine leaflet.

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**What Mefloquine is and what it is used for**

**Therapeutic indications**

Therapy and prophylaxis of malaria.

**Therapy:** Mefloquine is especially indicated for therapy of *P. falciparum* malaria in which the pathogen has become resistant to other antimalarial agents.

Following treatment of *P. vivax* malaria with Mefloquine, relapse prophylaxis with an 8-amino-quinoline derivative, for example primaquine, should be considered in order to eliminate parasites in the hepatic phase.

**Prophylaxis:** Malaria prophylaxis with Mefloquine is particularly recommended for travellers to malarious areas in which multiple resistant *P. falciparum* strains occur.

For current advice on geographical resistance patterns and appropriate chemoprophylaxis, current guidelines or the Malaria Reference Laboratory should be consulted, details of which can be found in the British National Formulary (BNF).

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**Dosage and method of administration**

**Curative treatment**

The recommended total therapeutic dose of mefloquine for non-immune patients is 20 – 25mg/kg. A lower total dose of 15mg/kg may suffice for partially immune individuals.

The recommended total therapeutic dosages of Mefloquine tablets relative to body weight and immune status are presented in the following table.*

<table>
<thead>
<tr>
<th>Non-immune patients</th>
<th>Partially immune patients</th>
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</thead>
<tbody>
<tr>
<td>&lt; 20kg **</td>
<td>½ tablet / 2.5 – 3kg</td>
</tr>
<tr>
<td></td>
<td>1 tablet / 10 – 12 kg</td>
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<tr>
<td>20 – 30kg</td>
<td>2 – 3 tablets</td>
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<tr>
<td>&gt; 30 – 45kg</td>
<td>3 – 4 tablets</td>
</tr>
<tr>
<td>&gt; 45 – 60kg</td>
<td>4 – 5 tablets</td>
</tr>
<tr>
<td>&gt; 60kg ***</td>
<td>6 tablets</td>
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</tbody>
</table>

* Splitting the total curative dosage into 2 – 3 doses (e.g. 3 + 1, 3 + 2 or 3 + 2 + 1 tablets) taken 6 – 8 hours apart may reduce the occurrence or severity of adverse events.

**Experience with Mefloquine in infants less than 3 months old or weighing less than 5kg is limited.**

*** There is no specific experience with total dosages of more than 6 tablets in very heavy patients.

A second full dose should be given to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30 – 60 minutes after a dose, an additional half-dose should be given.

If a full treatment course with Mefloquine does not lead to improvement within 48 – 72 hours, alternative treatments should be considered. When breakthrough malaria occurs during Mefloquine prophylaxis, physicians should carefully evaluate which antimalarial to use for therapy.

Mefloquine can be given for severe acute malaria after an initial course of intravenous quinine lasting at least 2 – 3 days. Interactions leading to adverse events can largely be prevented by allowing an interval of at least 12 hours after the last dose of quinine.

In areas with multi-resistant malaria, initial treatment with artemisinin or a derivative, if available, followed by Mefloquine is also an option.

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**Malaria prophylaxis**

For malaria prophylaxis the stated dose of Mefloquine should be given once weekly, always on the same day. Treatment should be initiated at least one week and up to 2-3 weeks before arrival in a malarious area and continued for 4 weeks after leaving (minimum treatment period 6 weeks). The maximum recommended duration of administration of Mefloquine is 12 months.

The following dosage schedule is given as a guide.

<table>
<thead>
<tr>
<th>Dosage</th>
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</thead>
<tbody>
<tr>
<td>Adults and children of more than 45kg bodyweight</td>
</tr>
<tr>
<td>Children and adults weighing less than 45kg</td>
</tr>
<tr>
<td>5 – 19kg</td>
</tr>
<tr>
<td>20 – 30kg</td>
</tr>
<tr>
<td>31 – 45kg</td>
</tr>
</tbody>
</table>

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**Elderly**

No specific adaptation of the usual adult dosage is required for elderly patients.

**Contraindications**

Prophylactic use in patients with severe impairment of liver function should be regarded for the time being as a contraindication as no experience has been gained in such patients.

Patients with a history of psychiatric disturbances (including depression) or convulsions should not be prescribed Mefloquine prophylactically, as it may precipitate these conditions.

Mefloquine should not be administered to patients with a known hypersensitivity to mefloquine or related compounds, e.g. quinine.

Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine must not be given simultaneously with or subsequent to Mefloquine. No data are available where Mefloquine was given after halofantrine.

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**Special warnings and precautions for use**

Women of childbearing potential travelling to malarious areas in which multiple resistant *P. falciparum* is found and who are receiving Mefloquine for the treatment and prophylaxis of malaria should take reliable contraceptive precautions for the entire duration of therapy and for three months after the last dose of Mefloquine.

If psychiatric disturbances occur during prophylactic use, Mefloquine should be discontinued and an alternative prophylactic agent should be recommended.

Experience with Mefloquine in infants less than 3 months old or weighing less than 5kg is limited. There is no evidence that dose adjustment is necessary for patients with renal insufficiency. However, since clinical evidence in such patients is limited, caution should be exercised when using Mefloquine in patients with impaired renal function.

In patients with epilepsy, mefloquine may increase the risk of convulsions. Therefore in such cases, Mefloquine should be used only for curative treatment and only if compelling reasons exist.

Mefloquine should be taken with caution in patients suffering from cardiac conduction disorders, since transient cardiac conduction alterations have been observed during curative and preventative use. Due to the risk of a potentially fatal prolongation of the QTc interval, halofantrine must not be given during Mefloquine therapy for prophylaxis or treatment of malaria, or within 15 weeks after the last dose of Mefloquine. Due to increased plasma concentrations and elimination half-life of mefloquine following co-administration with ketoconazole, the risk of QTc prolongation may also be expected if ketoconazole is taken during Mefloquine therapy for prophylaxis or treatment of malaria, or within 15 weeks after the last dose of Mefloquine.

Patients should not disregard the possibility that re-infection or recrudescence may occur after effective antimalarial therapy.

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Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicinal products and other forms of interaction

Concomitant administration of Mefloquine and other related compounds (e.g. quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and increase the risk of convulsions. There is evidence that the use of halofantrine during Mefloquine therapy for prophylaxis or treatment of malaria, or within 15 weeks after the last dose of Mefloquine, causes a significant lengthening of the QTc interval. Clinically significant QTc prolongation has not been found with melfoquine alone.

This appears to be the only clinically relevant interaction of this kind with Mefloquine, although theoretically co-administration of other drugs known to alter cardiac conduction (e.g. anti-arrhythmic or β- adrenergic blocking agents, calcium channel blockers, antihistamines or H1-blocking agents, tricyclic antidepressants and phenothiazines) might also contribute to a prolongation of the QTc interval.

In patients taking an anticonvulsant (e.g. valproic acid, carbamazepine, phenobarbital or phenytoin), the concomitant use of Mefloquine may reduce seizure control by lowering the plasma levels of the anticonvulsant. Dosage adjustments of anti-seizure medication may be necessary in some cases. When Mefloquine is taken concurrently with oral live typhoid vaccines, attenuation of immunisation cannot be excluded. Vaccinations with oral attenuated live bacteria should therefore be completed at least 3 days before the first dose of Mefloquine.

Other Potential Interactions

Mefloquine does not inhibit or induce the cytochrome P450 enzyme system. It is therefore not expected that the metabolism of drugs given concomitantly with melfoquine is affected. However, inhibitors or inducers of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of melfoquine, leading to an increase or decrease in melfoquine plasma concentrations, respectively.

Inhibitors of CYP3A4

One pharmacokinetic study in healthy volunteers showed that the co-administration of ketoconazole, a strong inhibitor of CYP3A4, increased the plasma concentrations and elimination half-life of melfoquine.

Inducers of CYP3A4

The long-term use of rifampicin, a potent inducer of CYP3A4, reduced the plasma concentrations and elimination half-life of melfoquine.

Substrates and inhibitors of P-glycoprotein

It has been shown in vitro that melfoquine is a substrate and an inhibitor of P-glycoprotein. Therefore, drug-drug interactions could also occur with drugs that are substrates, or are known to modify the expression of this transporter. The clinical relevance of these interactions is not known to date.

No other drug interactions are known. Nevertheless, the effects of Mefloquine on travellers receiving co - medication, particularly those on anticoagulants or antidiasbetics, should be checked before departure.

Pregnancy and lactation

Mefloquine has been shown to be teratogenic in mice and rats and embryotoxic in rabbits. Data from a limited number of exposed pregnancies indicate no adverse effects of melfoquine on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available.

Mefloquine should not be used during pregnancy particularly in the first trimester unless the expected benefit justifies the potential risk to the foetus.

Women of childbearing potential should be advised to practice contraception during malaria prophylaxis with Mefloquine and for up to 3 months thereafter.

As melfoquine is secreted into the breast milk, nursing mothers should not breast-feed while taking Mefloquine.

Effects on ability to drive and use machines

Mefloquine can cause dizziness or disturbed sense of balance. It is consequently recommended not to drive or carry out tasks demanding fine co-ordination and spatial discrimination during treatment with melfoquine. Patients should avoid such tasks for at least 3 weeks following therapeutic use, as dizziness, a disturbed sense of balance or neuropsychiatric reactions have been reported up to 3 weeks after the use of Mefloquine.

Prophylactic use

Caution should be exercised with regard to driving, piloting aircraft and operating machines, as dizziness, a disturbed sense of balance or neuropsychiatric reactions have been reported during and up to three weeks after use of Mefloquine.

In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug.

Undesirable effects

At the doses given for acute malaria, adverse reactions to Mefloquine may not be distinguishable from symptoms of the disease itself. The overall incidence of adverse events reported during melfoquine prophylaxis is comparable to that reported for other chemoprophylactic regimens. However, the profile of melfoquine-adverse events is predominantly characterised by neuropsychological adverse events.

Because of the long half-life of melfoquine, adverse reactions to Mefloquine may occur or persist for more than several weeks after discontinuation of the drug. In a small number of patients, it has been reported that dizziness and vertigo and loss of balance may continue for months after discontinuation of the drug.

Patients should be advised to obtain medical advice before the next weekly dose of Mefloquine, if any concerning or neuropsychiatric symptoms develop.

Discontinuation of Mefloquine should be considered, particularly if neuropsychiatric reactions occur. The need for alternative antimalarial therapy or prophylaxis can then be evaluated.

The following adverse events have been reported, although their absolute frequencies are not known (cannot be estimated from the available data):

- Blood and Lymphatic System Disorders: Leucopenia or leucyctosis and thrombocytopenia.
- Immune System Disorders: There have been rare reports of anaphylaxis in patients taking Mefloquine.
- Metabolism and Nutrition Disorders: Anorexia.
- Psychiatric Disorders: Sleep disorders (insomnia, abnormal dreams), agitation, restlessness, anxiety, depression, mood swings, panic attacks, confusional state, hallucinations, aggression, psychotic or paranoid reactions.

There have been rare reports of suicidal ideation and suicide, but no relationship to drug administration has been established.

- Nervous System Disorders: Dizziness, loss of balance, headache and somnolence, syncope, convulsions, memory impairment, sensory and motor neuropathies (including paraesthesia, tremor and ataxia). Isolated cases of encephalopathy have been reported.
- Eye Disorders: Visual disturbances.
- Ear and Labyrinth Disorders: Vertigo, vestibular disorders including tinnitus and hearing impairment.
- Cardiac Disorders: Tachycardia, palpitation, bradycardia, irregular heart rate, extrasystoles, other transient cardiac conduction alterations. Isolated cases of AV-block have been reported.
- Vascular Disorders: Circulatory disturbances (hypotension, hypertension, flushing).
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnoea. Very rare cases of pneumonitis of possible allergic etiology have been reported.
- Gastrointestinal Disorders: Nausea, vomiting, diarrhoea and abdominal pain, dyspepsia.
- Hepatobiliary disorders: Transient elevation of transaminases. Skin and Subcutaneous Tissue Disorders: Rash, exanthema, erythema, urticaria, pruritus, alopecia, hyperhidrosis. Isolated cases of erythema multiforme and Stevens-Johnson syndrome have been reported.
- Musculoskeletal and Connective Tissue Disorders: Muscle weakness, muscle cramps, myalgia, arthralgia.
- General Disorders and Administration Site Disorders: Oedema, chest pain, asthma, malaise, fatigue, chills, pyrexia.

Studies in vitro and in vivo showed no haemolysis associated with G6PD deficiency.

Symptoms and signs

In cases of overdosage with Mefloquine, the symptoms mentioned may be more pronounced.

Treatment

Patients should be managed by symptomatic and supportive care following Mefloquine overdose. There are no specific antidotes. The use of oral activated charcoal to limit mefloquine absorption may be considered within one hour of ingestion of an overdose. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disorders.