Module 1.3.1.1: APPROVED PROFFESIONAL INFORMATION FOR MEFLIAM (TABLETS)

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

MEFLIAM (Tablets)

COMPOSITION:

Each tablet contains mefloquine hydrochloride equivalent to mefloquine 250 mg.

Inactive ingredients include colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, polysorbate 80, povidone, starch and talc.

Contains lactose monohydrate: 193 mg per tablet.

PHARMACOLOGICAL CLASSIFICATION:

A. 20.2.6 Medicines against protozoa.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mefloquine is a quinoline methanol derivative, structurally related to quinine. Mefloquine is a blood schizontozide with effects on the asexual blood forms of the malarial pathogens that affect humans (*Plasmodium falciparum, P. vivax*). It is also active against the gametocytes of *P. vivax*. Its mechanism of action is unknown. Mefloquine has no effect on the hepatic stage of malaria parasites.

Strains of *P. falciparum* resistant to mefloquine have been reported. Resistance to mefloquine may occur in any endemic area. Mefloquine resistance have been described. Resistance patterns occur and vary from region to region and with time. Cross-resistance between halofantrine and mefloquine and cross-resistance between mefloquine and quinine has been observed.

Pharmacokinetic properties:

Absorption:

The rate and extent of absorption of mefloquine is significantly enhanced by the presence of food in the stomach which leads to about a 40 % increase in bioavailability. The maximum plasma concentration after a single oral dose is reached in 6 to 24 hours (median 17 hours). The achieved plasma concentration in micrograms per litre is roughly equivalent to the dose in milligrams. At steady state with weekly doses of 250 mg, maximum plasma concentrations of 1 000 – 2 000 ng/mℓ have been recorded after 7 – 10 weeks.

Distribution:

Mefloquine is 98 % bound to plasma proteins and has a large apparent volume of distribution (13,5 – 29,1 ℓ/kg). Mefloquine crosses the placenta. Approximately 3 – 4 % of a 250 mg dose is excreted into breast milk.

Metabolism:

Two mefloquine metabolites have been identified in humans. The main metabolite of mefloquine, 2,8-bistrifluoromethyl-4-quinoline carboxylic acid, is inactive against *P. falciparum*. Clinical studies have demonstrated that the carboxylic acid metabolite

appears in plasma 2 – 4 hours after a single oral dose. Maximum plasma concentrations, which are approximately 50 % higher than those of mefloquine, are obtained after 2 weeks. Thereafter, plasma concentrations of mefloquine and its main metabolite decline at a similar rate. The main metabolite's area under the plasma-concentration-time curve is 3 – 5 times larger than that of the parent compound. The second metabolite, an alcohol, is present in minute quantities only.

Elimination:

It appears that mefloquine is mainly excreted into bile and faeces. In healthy adults mefloquine's mean elimination half-life varies between 2 and 4 weeks, with an average of approximately 3 weeks.

Total clearance, which is basically hepatic, is in the order of 30 mℓ/min. In volunteers urinary excretion of unchanged mefloquine and its main metabolite accounted for about 9 % and 4 % of the dose, respectively. Levels of other metabolites are not measurable in the urine.

Pharmacokinetics in special populations:

Children and the elderly:

No relevant age-related changes have been observed in the pharmacokinetic properties of mefloquine.

Patients with renal impairment:

No pharmacokinetic studies have been conducted in patients with renal insufficiency. Mefloquine and its main metabolite are not removed by haemodialysis to an appreciable extent. No special chemoprophylactic dosage adjustments are indicated

for dialysis patients to reach plasma concentrations similar to those in healthy people.

Long-term use:

The pharmacokinetic properties of mefloquine may be altered in acute malaria. During long-term prophylaxis, mefloquine's elimination half-life remains unchanged.

INDICATIONS:

- **MEFLIAM** tablets are indicated for prophylaxis of *Plasmodium falciparum* malaria, in regions where *P. falciparum* strains resistant to 4-aminoquinolines (e.g. chloroquine) occur.
- **MEFLIAM** may be effective against malaria parasites resistant to proguanil, pyrimethamine-sulphonamide combinations.

CONTRAINDICATIONS:

MEFLIAM is contraindicated in:

- Patients with known hypersensitivity to mefloquine or related compounds (e.g. quinine and quinidine) or any of the inactive substances contained in the formulation.
- Patients with depression or a past history of depression, generalised anxiety disorder, psychosis including schizophrenia, or other psychiatric disturbances.
- Patients with a history of convulsions.
- Children with body weight less than 5 kg.
- Patients with impaired renal or hepatic function, since safety has not been demonstrated.

- Pregnancy since teratogenicity was demonstrated in animal studies (see **"PREGNANCY AND LACTATION"**).
- Lactation as approximately 3 – 4 % of a 250 mg dose is excreted into breast milk (see **"PREGNANCY AND LACTATION"**).

Quinine and quinidine are contraindicated when **MEFLIAM** prophylaxis has been used.

WARNINGS AND SPECIAL PRECAUTIONS:

Neuropsychiatric adverse reactions:

MEFLIAM may cause psychiatric symptoms in some patients, ranging from anxiety, paranoia and depression to more serious hallucinations and psychotic behaviour. In some instances, these symptoms have continued long after **MEFLIAM** was stopped. Cases of suicide and suicidal ideation have been reported, although no causal relationship with mefloquine has been confirmed. To minimise the chances of these adverse events, **MEFLIAM** should be avoided in patients with depression or a past history of depression, generalised anxiety disorder, psychosis, including schizophrenia or other psychiatric disturbances.

If psychiatric symptoms such as unexplained anxiety, depression, restlessness or confusion are evident during **MEFLIAM** prophylaxis, **MEFLIAM** must be discontinued and alternative prophylaxis instituted, as these could be prodromal to a more serious neuropsychiatric event.

Because of the long half-life of mefloquine, adverse reactions to **MEFLIAM** may occur or persist up to several weeks after the last dose.

Quinine and quinidine are contraindicated when **MEFLIAM** prophylaxis has been used (see **"CONTRAINDICATIONS"**).

Hypersensitivity:

- **MEFLIAM** may cause hypersensitivity reactions, which may vary from mild cutaneous reactions to anaphylaxis (see **"CONTRAINDICATIONS"**).

Seizure disorders:

- **In epileptic patients, MEFLIAM may increase the risk of convulsions (see "CONTRAINDICATIONS").**

Cardiac toxicity:

- **MEFLIAM should be used with caution in patients suffering from cardiac conduction diseases such as asymptomatic sinus bradycardia and/or other conduction abnormalities.**
- Concomitant administration of **MEFLIAM** and other related compounds (quinine, quinidine and chloroquine) may produce ECG abnormalities and increase the risk of convulsions.
- **MEFLIAM** and halofantrine used simultaneously may lead to a potentially fatal prolongation of the QTc interval.

Contraceptive measures:

- As teratogenicity has been shown in animal studies, reliable contraception is recommended whilst taking **MEFLIAM** tablets and for three months after the last dose. Data on human exposure during the first trimester are insufficient to conclude safety in pregnancy (see **"CONTRAINDICATIONS"** and **"PREGNANCY AND LACTATION"**).

Eye disorders:

- Treatment with **MEFLIAM** may be associated with an increased risk of eye disorders including cataract, retinal disorders and optic neuropathy which may occur during or after treatment. These eye disorders can present with visual impairment and blurred vision (see **"SIDE-EFFECTS"**). In some cases the event resolved very slowly but there have been reports of permanent sequelae.
- Any patient on treatment with **MEFLIAM** who experiences visual disorders should be referred to his/her treating medical practitioner, as certain conditions (such as retinal disorders or optic neuropathy) may require stopping treatment with **MEFLIAM**.
- Periodic ophthalmic examinations should be done regularly with long-term use.

Long-term use:

- **MEFLIAM** has not been administered for longer than 1 year. If administered for a prolonged period (longer than 3 months), periodic monitoring, including liver function tests, should be performed.

Toxic encephalopathy:

- **MEFLIAM** may cause toxic encephalopathy of unknown aetiology during prophylaxis.

Resistance:

- **MEFLIAM** prophylaxis should not exceed three months as long-term prophylaxis is thought to contribute to the development of resistant strains of *P. falciparum*.
- Resistance to mefloquine, as in **MEFLIAM**, has been documented in some areas.

Impaired liver or renal function:

- In patients with liver impairment the elimination of **MEFLIAM** may be prolonged, leading to higher plasma concentrations (see **"CONTRAINDICATIONS"**).
- Caution is advised in patients with compromised renal or hepatic function, and in elderly patients as there may be different pharmacokinetic parameters for these groups (see **"CONTRAINDICATIONS"**).

Additional preventative measures:

Preventative medication with **MEFLIAM** is not 100 % effective, the following measures to prevent mosquitoes from biting should be taken to reduce the risk of contracting malaria:

- Visit endemic areas during the dry season or in years when rainfall is low.

- High risk persons should avoid malaria areas altogether. High risk individuals include:
    - Babies and young children less than 5 years of age.
    - Pregnant patients.
    - Immunocompromised individuals, such as those on long-term steroids, cancer patients, chemotherapy patients, AIDS patients and those who have had their spleen removed.
- Do not go outside between dusk and dawn, when mosquitoes are most active.
- Apply insect repellent to exposed skin and clothes.
- Wear long sleeves and long trousers at night.
- Use mosquito nets, screens, coils and pads.

If flu-like symptoms develop in patients who have been in a malaria area they should inform their doctor accordingly, as malaria may initially present with flu-like symptoms.

Effects on ability to drive or use machines:

Caution must be exercised during driving, piloting aircraft, scuba diving, mountain climbing, hiking and biking and operating machines as dizziness, disturbed sense of balance or neuropsychiatric reactions have been reported whilst taking **MEFLIAM** and for three weeks afterwards.

Lactose:

MEFLIAM contains lactose. Patients who are lactose intolerant and who take **MEFLIAM** may experience unwanted side effects, such as nausea, cramping,

bloating, diarrhoea, and flatulence. **MEFLIAM** should not be administered to patients with hereditary galactose intolerance e.g. galactosaemia, glucose-galactose malabsorption or with the rare Lapp lactase deficiency.

INTERACTIONS:

Concurrent use of beta-blockers, calcium channel blocking agents, antihistamines or H_1-blocking agents, tricyclic antidepressants and phenothiazines, quinidine or quinine with **MEFLIAM** tablets may result in sinus bradycardia, prolonged QTc intervals or cardiac arrest.

The risk of seizures may also be increased with quinine, quinidine and chloroquine; concurrent use should therefore be avoided. If concurrent use is necessary, close monitoring of patient response is recommended. In addition, patients should be advised to take **MEFLIAM** at least 12 hours after the last dose of quinidine or quinine.

MEFLIAM and halofantrine used simultaneously may lead to a potentially fatal prolongation of the QTc interval (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

MEFLIAM may lower serum concentrations of anticonvulsants (e.g. valproic acid, carbamazepine, phenobarbital or phenytoin) and cause loss of seizure control. Monitoring of these anticonvulsant serum concentrations is recommended and dosage adjustments may be necessary during and after prophylaxis with **MEFLIAM**.

The concurrent use of the oral typhoid vaccine with **MEFLIAM** may decrease the effectiveness of the oral typhoid vaccine; doses of the two medications should be separated by 7 to 10 days. It must be remembered that the first dose of **MEFLIAM** should be taken one week before entering the malaria area.

Patients who are taking anticoagulants (such as warfarin), and oral antidiabetic agents (such as metformin, glimepiride, glipizide or pioglitazone) should be monitored and have the relevant parameters checked [such as prothrombin time / INR (International Normalised Ratio) or blood sugar levels] before taking these with **MEFLIAM**, as it is not known whether there are any other interactions.

PREGNANCY AND LACTATION:

Pregnancy:

MEFLIAM is contraindicated in pregnancy and lactation (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"CONTRAINDICATIONS"**).

Teratogenicity in animals has been demonstrated with **MEFLIAM** use. There is insufficient data on human exposure during the first trimester to conclude safety in pregnancy.

Women of childbearing potential:

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

Lactation:

MEFLIAM is excreted into breast milk and therefore if it must be taken, breastfeeding should be discontinued (see **"CONTRAINDICATIONS"**).

DOSAGE AND DIRECTIONS FOR USE:

The recommended prophylactic dose of **MEFLIAM** is approximately 5 mg/kg once weekly.

The following weekly doses of **MEFLIAM** are recommended:

Body weight:	**Weekly dose for prophylaxis:**
5 – 19 kg	¼ tablet (62,5 mg)
20 – 30 kg	½ tablet (125 mg)
31 – 45 kg	¾ tablet (187,5 mg)
> 45 kg	1 tablet (250 mg)

Experience with **MEFLIAM** in infants less than 3 months old or weighing less than 5 kg does not exist.

The dosage for children has been extrapolated from the recommended adult dose.

The first dose should be taken one week before arrival in an endemic area and subsequent weekly doses should be taken on the same day of each week. In certain instances, e.g. when a traveller is taking other medicines, it may be desirable to initiate prophylaxis 2 – 3 weeks before departure in order to ensure that the combination of medication is well tolerated.

Prophylaxis should be continued for four weeks after leaving the malarial area, and should not exceed 3 months' duration.

The tablets should be swallowed whole after food with plenty of fluids. The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other people who are not able to swallow them whole. **MEFLIAM** is bitter and has a slightly burning taste.

SIDE EFFECTS:

Blood and lymphatic system disorders:

Frequency unknown:	Leucopenia or leucocytosis and thrombocytopenia.

Psychiatric disorders:

Frequent:	Emotional problems.
Less frequent:	Neuropsychiatric toxicity (including anxiety, confusion, depression, hallucinations, psychotic manifestations, such as mood or mental changes, mental depression, and/or restlessness), and sleep disturbances, such as abnormal dreams and insomnia, and asthenia (feeling of weakness) and psychological changes.
Frequency unknown:	Somnolence, and paraesthesia.

Psychiatric reactions, sometimes disabling and prolonged, have been reported in association with **MEFLIAM**. These include, apart from those mentioned above,

aggression, agitation, emotional instability, forgetfulness, sensory and motor neuropathies (including ataxia, paraesthesia and tremor), panic attacks, paranoia, and psychosis. Cases of suicidal ideation and suicide have been reported, although no causal relationship with **MEFLIAM** has been established.

Nervous system disorders:

Frequent:	Headache.
Less frequent:	Central nervous system disturbances, encephalopathy.
Frequency unknown:	Seizures (convulsions), sensory and motor neuropathies (including paraesthesia and tremor), and ataxia.

Eye disorders:

Frequent:	Visual impairment (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
Frequency unknown:	Visual disturbances, blurred vision, cataract, retinal disorders and optic neuropathy which may occur gradually during or after treatment (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Ear and labyrinth disorders:

Frequent:	Dizziness or disturbed sense of balance, tinnitus.
Frequency unknown:	Hearing impairment.

Cardiac disorders:

Less frequent:	Bradycardia and dysrhythmia.
Frequency unknown:	Atrioventricular block, extrasystoles and irregular pulse, palpitations, transient cardiac conduction alterations, chest pain, tachycardia, oedema and syncope.

Vascular disorders:

Frequency unknown:	Hypertension, hypotension, flushing.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown:	Dyspnoea.

Gastrointestinal disorders:

Frequent:	Abdominal pain, loose stools or diarrhoea, nausea, vomiting.
Less frequent:	Anorexia.
Frequency unknown:	Dyspepsia.

Hepatobiliary disorders:

Frequency unknown:	Transient elevation of transaminases.

Skin and subcutaneous tissue disorders:

Less frequent:	Erythema multiforme, Stevens-Johnson syndrome, and alopecia.

Frequency unknown: Pruritus, rash, urticaria, erythema, xanthema, and sweating.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia and/or arthralgia.

Frequency unknown: Muscle cramps or weakness.

General disorders and administrative site conditions:

Frequent: Fever, chills.

Frequency unknown: Fatigue, malaise.

These adverse events can be observed several weeks after the last dose has been taken.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the event of an overdose with **MEFLIAM**, the symptoms would be those specified under **"SIDE EFFECTS"** but more pronounced. There is no known specific antidote for an overdosage. Treatment should include standard gastric decontamination procedures and routine symptomatic and supportive treatments, particularly for cardiovascular disturbances. Cardiac function, neurological and psychiatric status should be monitored for at least 24 hours.

IDENTIFICATION:

Flat, white, circular uncoated tablets with bevelled edges. One side has a cross breakline and the other side is plain.

PRESENTATION:

MEFLIAM tablets are available in blister packs of 6 and 8 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

31/20.2.6/0502

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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