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**Recommendations for the treatment of
Onchocerciasis with Mectizan®
in areas co-endemic
for Onchocerciasis and Loiasis**

**The Mectizan® Expert Committee
and
The Technical Consultative Committee**

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The Mectizan® Expert Committee/Technical Consultative Committee

Recommendations for the treatment of onchocerciasis with Mectizan® in areas co-endemic for Onchocerciasis and Loiasis

Background:

The most important risk encountered in distributing Mectizan® for the control of onchocerciasis in areas where *Loa loa* is co-endemic is the development of an encephalopathic syndrome in people with very high levels of *L. loa* [$> 30,000$ microfilariae/milliliter blood (mf/ml)] following treatment with Mectizan®. This syndrome, which occurs rarely, is characterized by symptoms such as confusion, lethargy, coma, and urinary incontinence.

The reason this syndrome develops is that Mectizan®, in addition to being an effective drug against the microfilariae of *Onchocerca volvulus* (the causative agent of onchocerciasis), is also effective against *L. loa* microfilariae, the rapid killing of which has been associated with this encephalopathy. Like all serious illnesses, this encephalopathy requires prompt medical and nursing care to provide supportive treatment and to prevent nosocomial infections. With competent and timely medical care, patients usually recover fully. The pathogenesis of this encephalopathy remains unknown.

L. loa is known, or suspected, to be endemic in humid forest areas of Central and East Africa. The precise distribution of *L. loa* is still being defined and mapped. Methodologies for mapping include parasitologic surveys, rapid assessment of *L. loa* based on the restricted definition of eye worm passage (RAPLOA), and predicted prevalence based on environmental factors conducive to the breeding of the vector of *L. loa*, *Chrysops spp.*

Recent epidemiologic studies have shown that in areas where the prevalence of *L. loa* microfilaremia in adults exceeds 20%, the percentage of adults with *L. loa* microfilaremia greater than 30,000 mf/ml is about 1%.¹ The threshold for increased community risk of *L. loa* encephalopathy following Mectizan® treatment has been defined as 20% microfilaremia prevalence which corresponds to a 40% prevalence of history of eye worm passage as measured by RAPLOA.²

¹ Boussinesq M, Gardon J, Chippaux JP. Relationships between the prevalence and intensity of *Loa loa* infection in the Central province of Cameroon. *Annals of Tropical Medicine & Parasitology* 2001, 95:495-507.

² Takougang I, Meremikwu M, Wandji S, Yenshu E, Aripko B, Lamle S, Braide E, Enyong P, Meli J, Kale O, Remme J. Rapid assessment method for prevalence and intensity of *Loa loa* infection. *Bulletin of the World Health Organization* 2002, 80(11):852-858.

Recommendations:

The following recommendations from the Mectizan® Expert Committee/Technical Consultative Committee are intended to facilitate effective detection and management of serious adverse events (SAEs) and their complications, should they occur, following treatment with Mectizan® in, known and suspected, *L. loa* endemic areas. The table below summarizes the main points.

Decision Table:

Onchocerciasis Endemicity (confirmed by completed REMO)	Loias is Endemicity	Recommended Mass Distribution Strategy
Hyper-/meso-endemic	Non-endemic	Proceed with routine Mectizan® mass treatment procedures
Hyper-/meso-endemic	Suspected <i>L. loa</i>	Assess <i>L. loa</i> endemicity before mass distribution of Mectizan® and proceed with appropriate strategy
Hyper-/meso-endemic	<ul style="list-style-type: none"> • <i>L. loa</i> mf prevalence: < 20% OR • Prevalence of history of eye worm passage (RAPLOA): < 40% 	Implement Strategy 2*
Hyper-/meso-endemic	<ul style="list-style-type: none"> • <i>L. loa</i> mf prevalence: ≥ 20% OR • Prevalence of history of eye worm passage (RAPLOA): ≥ 40% 	Implement Strategy 1*
Hypo-endemic	Non-endemic	Individual treatment with Mectizan®
Hypo-endemic	Known or suspected <i>L. loa</i>	Implement Strategy 3*

*Strategies 1, 2, and 3 are detailed on the following pages.

A. AREAS MESO- or HYPER-ENDEMIC FOR ONCHOCERCIASIS:

STRATEGY 1:

The Mectizan® Expert Committee/Technical Consultative Committee recommends that, for onchocerciasis control programs operating in areas confirmed as meso- or hyper-endemic for onchocerciasis and known, or suspected, to have L. loa microfilaremia prevalence of ³ 20% OR prevalence of history of eye worm passage (RAPLOA) of ³ 40%, the following measures must be taken before and during mass distribution of Mectizan®:

- a. Enhance community awareness and education with regard to recognizing, responding to, and referring cases of SAEs following treatment with Mectizan® to a designated health facility for clinical management of such cases.
- b. Enhance awareness and training of community distributors and all health personnel involved in the program with regard to recognizing, responding to, and referring cases of SAEs following treatment with Mectizan® to a designated health facility for clinical management of such cases.
- c. Teams of medical personnel should be trained at all designated health facilities so that the strategy of clinical management of SAE cases, as recommended in *Appendix A*, is understood by all responsible for clinical care.
- d. All designated health facilities should be equipped with medical supplies appropriate for SAE case management. Please see *Appendix B* for a recommended list of medical supplies.
- e. Mass distribution of Mectizan® should be implemented following these guidelines:
 - i. Distribution during a fixed period of time in a season of the year when travel is least encumbered by weather (e.g. heavy rain).
 - ii. The period of treatment and the geographic location of communities to be treated should be organized to allow for the recommended post-treatment surveillance, as follows:
 1. Careful observation of community members by community distributors for days 2-8 after treatment, where day 1 is defined as the day of treatment;
 2. Surveillance by medical personnel for days 3-5 after treatment.
 - iii. Individuals developing SAEs following treatment with Mectizan®, such as encephalopathy, should be referred to a designated health facility where management according to the guidelines in *Appendix A* can be carried out. Family members should be encouraged to accompany the patient and provide basic support.

NOTE:

*1) If 2 or more rounds of Mectizan® distribution have occurred in the treatment area, both with treatment of ³ 65% of the total population and with no cases of *L. loa* encephalopathy following treatment with Mectizan® being reported, then Strategy 2 below can be implemented in place of Strategy 1 during the 3rd and subsequent rounds of treatment provided no cases occur.*

*2) In certain situations where many rounds of Mectizan® distribution have occurred in the treatment area, with treatment of ³ 65% of the total population and with no cases of *L. loa* encephalopathy following treatment with Mectizan® being reported, programs may proceed with routine mass treatment procedures instead of Strategy 1 or 2.*

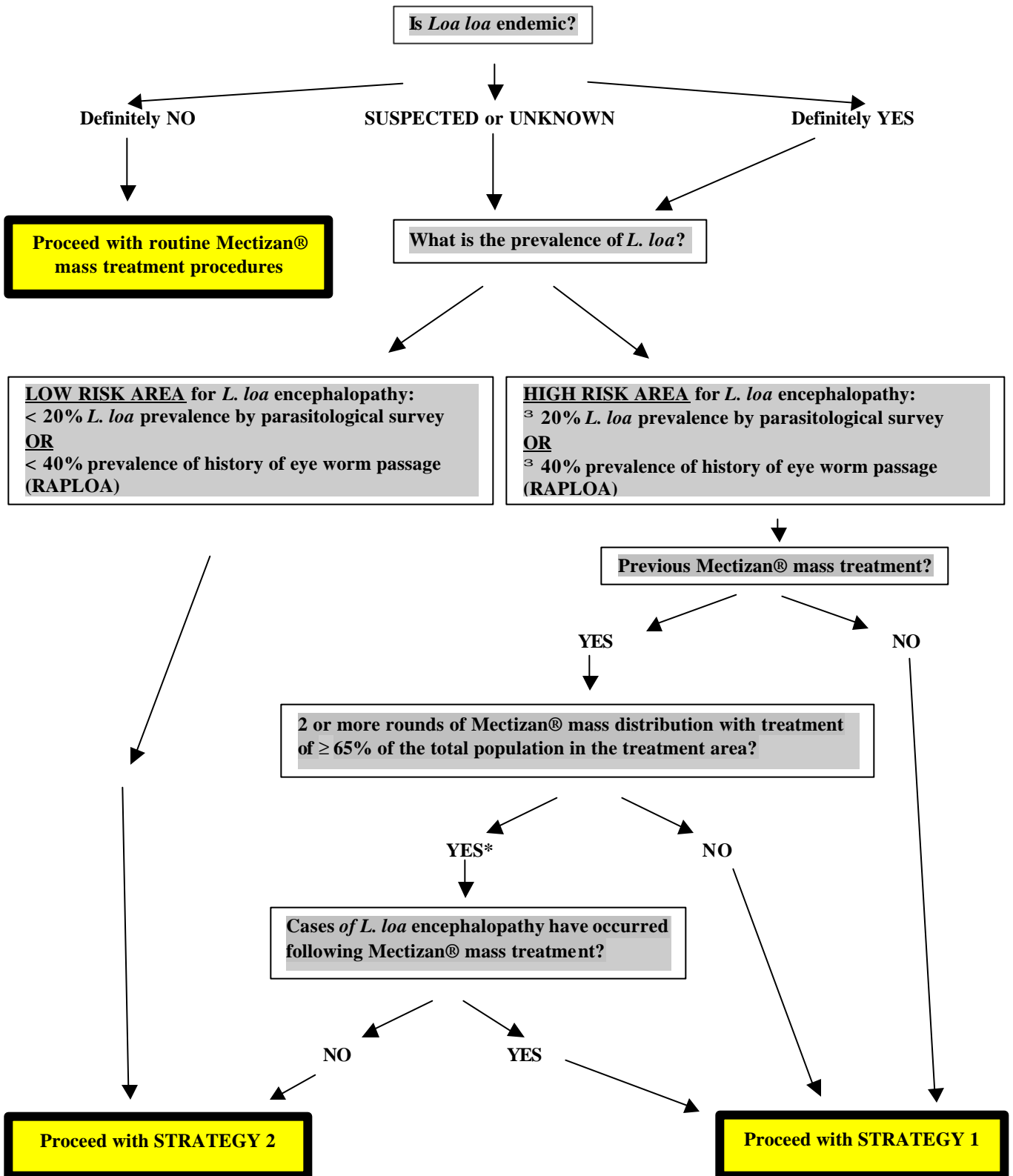
A. AREAS MESO- or HYPER-ENDEMIC FOR ONCHOCERCIASIS (continued):

STRATEGY 2:

The Mectizan® Expert Committee/Technical Consultative Committee recommends that, for onchocerciasis control programs operating in areas confirmed as meso- or hyper-endemic for onchocerciasis and known, or suspected, to have L. loa microfilaremia prevalence of < 20% OR prevalence of history of eye worm passage (RAPLOA) of < 40%, the following measures must be taken before and during mass distribution of Mectizan®:

- a. Enhance community awareness and education with regard to SAEs following treatment with Mectizan®.
- b. Enhance awareness and training of community distributors and all health personnel involved in the program with regard to recognizing, responding to, and referring cases of SAEs following treatment with Mectizan® to a health facility for clinical management of such cases.
- c. Report, immediately, any SAE case to the program coordinator for assessment of the situation.

A. AREAS MESO- or HYPER-ENDEMIC FOR ONCHOCERCIASIS (continued): Summary Algorithm



***NOTE:** In certain situations where many rounds of Mectizan® distribution have occurred in the treatment area, with treatment of [≥] 65% of the total population and with no cases of *L. loa* encephalopathy following treatment with Mectizan® being reported, programs may proceed with routine mass treatment procedures instead of Strategy 1 or 2.

B. AREAS HYPO-ENDEMIC FOR ONCHOCERCIASIS:

STRATEGY 3 (Individual, clinic-based treatment strategy):

The Mectizan® Expert Committee/Technical Consultative Committee recommends that, for onchocerciasis control programs operating in areas known to be hypo-endemic for onchocerciasis AND suspected of being, or known to be, endemic for L. loa, the following modified individual treatment strategy is warranted:

- a. Confirm infection with *O. volvulus* and assess the possibility of infection with *L. loa*. In the absence of hematologic diagnostic methods for *L. loa*, patients should be asked questions to determine if loiasis is probably present in their community of residence or employment.
- b. Prior to treating with Mectizan®, the possibility of developing *L. loa* encephalopathy following treatment with Mectizan® in people with high intensity *L. loa* infection should be discussed with the patient.
- c. Administer appropriate dose of Mectizan®.
- d. If the patient is at risk of *L. loa* encephalopathy following treatment with Mectizan®, he/she should be monitored by medical personnel after Mectizan® is administered as described in Strategy 1, section e.

The ultimate decision on how to proceed with community-based mass treatment of onchocerciasis with Mectizan®, in a given country, should be made by the National Onchocerciasis Task Force (NOTF) and the Ministry of Health, which has final authority and responsibility for all decisions. Moreover, the decision on how to proceed with the treatment of individuals with onchocerciasis in clinic-based settings is the responsibility of the individual physician.

Appendix A:

Mectizan® Expert Committee/Technical Consultative Committee

Guidelines for the clinical management of cases of *Loa loa* encephalopathy following treatment of onchocerciasis with Mectizan® in loiasis endemic areas

I. BACKGROUND

Encephalopathy following Mectizan® treatment of onchocerciasis in *Loa loa* endemic areas occurs rarely (less than 1 case/10,000 treatments). This encephalopathy is associated with a high *L. loa* microfilarial load prior to treatment, particularly greater than 30,000 microfilariae/milliliter of blood. The patient may initially present with severe fatigue, myalgia, arthralgia, low-grade fever, low back pain, difficulty standing up or walking before the onset of the encephalopathy, or they may initially present with signs of encephalopathy. The typical encephalopathic signs and symptoms of confusion, agitation, lethargy, dysarthria, mutism, and urinary incontinence usually appear 2 to 3 days after treatment with Mectizan® and are progressive, and may lead to coma in the worst cases. The presence of sub-conjunctival hemorrhages of the palpebral conjunctivae has been suggested as an early warning sign of the encephalopathy, but this requires further evaluation. In the meanwhile, patients presenting with this sign should be placed under surveillance.

There is no specific treatment for this encephalopathy; symptomatic treatment is normally sufficient to ensure full recovery in most patients. However, as some of these patients are often hospitalized for long periods (exceeding 10 days), they are at risk for the development of dehydration, denutrition, pressure ulcers, and nosocomial infections, which may lead to prolongation of hospitalization, worsening clinical condition, and sometimes death. Thus, sound medical and nursing practices are needed to optimize the care of the hospitalized patient.

II. CLINICAL MANAGEMENT

*Upon identification of a person with signs and symptoms suggestive of a *L. loa* encephalopathy following treatment with Mectizan®, the following measures are recommended:*

A. COMMUNITY

Evacuate the patient immediately to the nearest designated health facility for the management of serious adverse events (SAEs) following Mectizan® treatment.

B. HEALTH CENTRE

Evacuate the patient immediately to the nearest designated health facility for the management of SAEs following Mectizan® treatment, making sure to send on all relevant clinical and laboratory information, and if possible, inform the doctor(s) on duty there. Ensure that the patient is well hydrated, either parenterally or orally, during the referral process.

C. DESIGNATED HEALTH FACILITY FOR MANAGEMENT OF SAEs FOLLOWING MECTIZAN® TREATMENT

1. Assessment

(a) Clinical:

- i. A detailed clinical examination, including a neurologic exam, should be undertaken upon admission and repeated as needed depending on the patient's clinical status. Findings should be carefully documented, preferably on a standardized form from the Ministry of Health or National Onchocerciasis Task Force.

- ii. Monitoring and documentation of vital signs (temperature, pulse, blood pressure, and respiratory rate), neurologic status (including Glasgow Coma Score), and fluid balance should be performed regularly as needed.
- iii. **Differential Diagnosis of Coma** - Investigate and treat common causes of coma (e.g. malaria, meningitis, stroke, diabetes, etc.)

(b) Laboratory:

The following tests to determine the cause of the encephalopathy and other co-morbidities are recommended:

- i. **Blood** - Electrolytes, Blood Urea Nitrogen, Creatinine, Glucose
 - Complete Blood Count
 - **Two thick blood smears are essential:** one to screen for *L. loa* and *Mansonella perstans* and the other for *Plasmodium falciparum*. **These blood smears should be retained for future confirmation of diagnosis.**
- ii. **Urinalysis for evidence of infection**
- iii. **Cerebrospinal fluid analysis** for evidence of hemorrhage and/or infection. [In the case of *L. loa* encephalopathy the fluid is crystal clear, and *L. loa* microfilariae can often be detected after centrifugation.]
- iv. **Other tests as necessary**

2. Treatment

(a) Hydration

- i. Oral hydration is always preferred if possible. However, if the parental route is the only route available, isotonic fluids, such as Normal Saline (NS) and Lactated Ringers (LR) solution, are recommended to be administered according to local standards.
- ii. If necessitated by patient's level of consciousness or urinary incontinence, place a urinary condom or an indwelling urinary catheter and monitor fluid balance (intake and diuresis).

(b) Nutrition

- i. If patient is able to safely ingest food, nutrition *per os* is ideal. Otherwise, provide intravenous nutrition in the form of NS with 5% glucose or LR with 5% glucose for a few days.
- ii. If after a few days, the patient is still unable to safely ingest food, then place a nasogastric feeding tube. Enteral feeding with nutritionally-rich broths according to the local standards should then proceed.

(c) AVOID CORTICOSTEROIDS since they have not been shown to improve the clinical course and may in fact worsen the clinical condition due to increased risk of infection and/or gastrointestinal bleeding after prolonged corticosteroid use.

3. Nursing Care

If patient is in a coma, the following measures must be taken:

(a) Eye - Apply eye ointment, and tape the eyes with clear medical tape in order to avoid exposure keratitis.

(b) Skin - Prevent formation of pressure (decubitus) ulcers by:

- Keeping patient's skin clean and dry at all times.
- Reducing pressure on bony prominences such as the sacrum, coccyx, greater trochanter and lateral malleolus by means of pressure-reducing mattresses if available or otherwise, appropriate cushions.
- Avoiding dragging the patient across the sheets when moving them in bed as that may damage the skin. It is better to lift and re-position than to drag.
- Turning patient every 2 hours.
- **AVOIDING MASSAGE** since that easily damages the skin.

- If pressure ulcers occur, recommended **management** is as follows:
 - Assess the extent of the wound, and modify patient's positioning in bed to prevent exacerbation of the wound.
 - Cleanse the wound with physiologic and nontoxic agents such as normal saline, and debride the wound as needed to remove debris, devitalized tissue and eschar.
 - Dress the wound with non-adherent dressings that maintain adequate moisture in the wound bed without damaging the surrounding normal skin.
 - Administer analgesics as needed for pain.
 - Ensure adequate dietary intake of proteins to facilitate wound healing.

(c) **Respiratory** - Aspirate oral secretions with a 20cc syringe.
 - If necessary, ensure patent airway by placing an oropharyngeal cannula.

(d) **Urinary** - Place urinary condom or indwelling urinary catheter.
 - Change catheter on a regular basis per local standard protocol in order to reduce the risk of infection.
 - Minimize the duration of catheterization to avoid bacteruria.

4. Prevention of Nosocomial Infections

The key strategies for preventing nosocomial (hospital-acquired) infections in a comatose patient are to apply the principles of good nursing care outlined above and to mobilize the patient as soon as the clinical condition improves.

5. Treatment of Nosocomial Infections

Despite the best attempts, however, nosocomial infections may still develop. This is often indicated by a sudden rise in temperature. When this occurs, collect necessary samples for laboratory diagnosis and institute appropriate antibiotic and/or antimalarial curative treatment **IMMEDIATELY** according to local standard protocols.

If pressure ulcers become infected, in addition to the interventions listed under 3b, the following is also recommended:

- Administer antibiotics as needed (topical antibiotics appropriate for local infection but systemic antibiotics required for cellulitis, osteomyelitis, sepsis and other infectious complications).

6. Referral for Intensive Care

If the patient's clinical condition deteriorates to the point where their care will require resources beyond the capacity of the designated health facility, then arrange for safe evacuation of the patient to the nearest hospital where intensive care can be ensured, and if possible, inform the doctor(s) on duty there.

7. Reporting of Serious Adverse Event

Report the case as a Mectizan®-related SAE to the NOTF as soon as possible using the SAE reporting form provided by the Mectizan® Donation Program. The form should be completed by the responsible physician or nurse as soon as it is determined that the case in question is an SAE related to Mectizan® ingestion. The final outcome for the patient may be reported at a later stage, when leaving the hospital, or in the event of death.

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Appendix B:

Mectizan® Expert Committee/Technical Consultative Committee

Medical supplies recommended to be made available at designated health facilities for management of serious adverse events following treatment with Mectizan®

I. Equipment

(a) Clinical

- Intravenous catheters
- Needles
- Syringes
- Bronchial aspirators
- Nasogastric tubes
- Urinary condoms or urinary catheters
- Lumbar puncture kits
- Appropriate comfortable mattresses to prevent pressure ulcers to the extent possible

(b) Laboratory

- Microscope
- Microscopic slides
- Reagents (e.g. Giemsa)
- Non-heparinized capillaries for calibrated blood smear
- Tubes for laboratory sample collection (e.g. complete blood count, biochemistry, etc.)

II. Therapeutics

- Intravenous Fluids
- Analgesics
- Antipyretics
- Oral, intravenous, and topical antibiotics as appropriate to local standards
- Oral and intravenous antimalarials as appropriate to local standards