Guide for Donations of Mectizan® to Accelerate the Elimination of Lymphatic Filariasis in Countries Where Onchocerciasis Is Not Co-endemic

Version 1

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Mectizan Donation Program
Taskforce for Global Health
325 Swanton Way
Decatur, Georgia 30030
USA

Ph: +1 404 371 1460
Fax: +1 404 393 9042
Email: Mectizan@mectizan.org

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Annexes

1. Background

In November 2017, the World Health Organization (WHO) published a new guideline on alternative mass drug administration (MDA) regimens to eliminate lymphatic filariasis (LF)[1]. Adding to existing strategies, the new guideline recommends the addition of ivermectin to diethylcarbamazine (DEC) and albendazole (Alb) to accelerate the elimination of LF where **river blindness (onchocerciasis) is not co-endemic** based on the following criteria:

a) implementation units (IUs) that have not started or have fewer than 4 effective rounds of DEC and Alb;
b) IUs that have not met the appropriate epidemiological targets in sentinel and spot-check site surveys or in transmission assessment survey (TAS) despite meeting drug coverage targets;
c) communities where post-MDA or post-validation surveillance identifies infection suggesting local transmission.

2. Merck & Co., Inc., Kenilworth, N.J., U.S.A.'s Commitment

To support this new initiative, Merck (known as MSD outside of the United States and Canada) announced on November 30, 2017 an expansion to its Mectizan® (ivermectin) donation program to include communities eligible for the combination of ivermectin + DEC + Alb (IDA) as defined by the WHO in the criteria mentioned above. The company's commitment includes the following elements:

a) 100 million Mectizan® treatments (up to 280 million tablets) will be donated annually beginning in 2018 through 2025, subject to the authorization of the Mectizan Expert Committee (MEC) and the Mectizan Donation Program (MDP).
b) Requests will be reviewed and tablets allocated through a mechanism to be established by the MDP and the MEC.

[1] https://apps.who.int/iris/handle/10665/259381

c) The approved tablets will be shipped and delivered to the specified warehouse in the recipient countries free of charge.

3. Country eligibility to receive Mectizan® for IDA

3.1. Epidemiological eligibility

A country non co-endemic for onchocerciasis will be eligible to apply for Mectizan® for IDA in IUs that meet the following criteria, as defined in the WHO guidelines:

a) IUs that have not started or have fewer than 4 effective rounds of DEC + Alb;
b) IUs that have not met the appropriate epidemiological targets in sentinel and spot-check site surveys or in TAS despite meeting drug coverage targets as defined by WHO;
c) for communities where post-MDA or post-validation surveillance identified infection, suggesting local transmission

Given the number of tablets available for IDA through the expansion of the Mectizan Donation Program, priority will be given to IUs that meet criteria 3.1. b) and 3.1. c).

3.2. Political commitment by Country applying for Mectizan®

The commitment of the government of a given country to accelerate elimination will be detailed in a revision of the elimination master plan with a redefined new elimination target year and adoption of IDA as a strategy.

The government of a given country will agree to:

a) register the donated Mectizan® if required by the relevant national regulatory authorities;
b) ensure free entry of Mectizan® into the country without imposing duty, tax, or other costs
c) Endorse the agreement in Annex 2.

3.3. Ability to plan and successfully implement an effective IDA

Countries must demonstrate:

a) Explicit, time bound elimination target and a supporting plan to identify the cessation of Mectizan treatment;

b) Availability of adequate resources (financial and human);

c) Ability to distribute the medicines to achieve effective coverage:
   - o If applicable, history of MDA with high coverage
   - o Planning of activities demonstrating the potential to increase coverage, as required
     - Training of the health workers and the drug distributors
     - Social mobilization
     - Incentives for drug distributors (if applicable)
     - Modalities to ensure directly observed treatment
   - o Coverage quality assessment

d) Safety management of IDA-related adverse event (AE) preparedness, monitoring, management and reporting:
   - o Safety preparedness: training of the health personnel and community drug distributors on the detection and management of IDA-related AE cases;
   - o AE surveillance (at least during the first IDA round);
     - Community distributors to monitor for IDA-related AEs for at least the first 3 days following the MDA
   - o Reference of IDA-related serious AE cases to the nearest health center for management – without cost to the patient; Following reporting requirements for AEs according to the guidelines of the national pharmacovigilance system with copy to mectizan@mectizan.org.

4. Mectizan® application for IDA

4.1. Application form and submission

Countries will use the IDA version of the WHO Joint Request for Selected Preventive Chemotherapy Medicines (JRSM-IDA) form to apply for Mectizan® for IDA[2].

Within the time limits recommended by WHO[3], the application will be submitted to both:

a) the department of NTD of the WHO-Regional office along with supporting documents;
b) the Mectizan Donation Program along with:
   - the revised master plan with IDA adopted by the Ministry of Health (MoH) as strategy to eliminate LF
   - the annual plan including districts targeted for IDA and the strategy to implement IDA with effective coverage and post intervention Monitoring and Evaluation (M&E)
   - epidemiological evidence of eligibility for IDA for each district
   - signed agreement to receive and distribute Mectizan®

4.2. Review process

Applications for Mectizan® for IDA will follow the WHO Joint Application Process (JAP) review mechanism. However, the final decision regarding the number of IUs to be approved will be made by the Mectizan Expert Committee (MEC) based on the 280 million tablets allocated annually for IDA through 2025. MEC members will submit recommendations using the form in annex 3. Since the expanded donation for IDA is a special provision to facilitate access to ivermectin and accelerate elimination, all applications, either initial or re-applications, will be discussed among MEC members and a decision of whether or not to provide medicines reached.

[2] https://www.who.int/teams/control-of-neglected-tropical-diseases/preventive-chemotherapy/joint-application-package
[3] no later than 15 April or 15 August of the year preceding the year for which medicines are intended to be used.

4.3. **Approval and shipment process**

Applicants will be notified of the decision in writing. If approved, an approval notice will be sent, with copies to all partners. The approval notice triggers the shipment process. MDP will aim for shipments of Mectizan® to be delivered at least 1 month prior to the beginning of the MDA campaign.

4.4. **Re-application approval criteria**

Re-applications for Mectizan® to perform a second round of IDA will be prioritized. A third round will be based on the following conditions:

a) Successful implementation of the previous donations with high coverage; and
b) The monitoring and Evaluation (M&E) data justify the need to implement additional IDA MDAs

Annex 1: Adverse Event (AE) Report Form

(FOR USE AT DRUG ADMINISTRATION SITE IN PREVENTIVE CHEMOTHERAPY PROGRAMMES)

Country:	**Date Of Report:**	**ID No. (if available):**
Patient name and contact details:		
	Age:	**Sex** (M/F):
Treatment site (Village/District):		

Which drugs were administered?	**Dose administered**	**Brand and Manufacturer Name**	**Batch Number**	**Time and Date of treatment:** (hour, day/month/year)
□ albendazole				
□ azithromycin				
□ diethylcarbamazine (DEC)				
□ ivermectin				
□ mebendazole				
□ praziquantel				
□ other (specify)				

Explain the circumstances of past and concomitant treatment(s) with same or other medicines and when they were given (if applicable):

Time and date of onset of the adverse event:

Description of adverse event:
(Please describe clinical signs and symptoms and diagnosis if known)

Description of adverse event (cont):
(Please tick boxes as appropriate**)**

☐ death

☐ life-threatening

☐ in-patient hospitalization or prolongation of an existing hospitalization

☐ persistent or significant disability/incapacity

☐ birth defect

☐ none of the above

Past medical history and other relevant information:
(e.g., other diseases, suspected parasitic infections such as malaria or loiasis, laboratory results, dates of hospitalization or death, alcohol intake within 24 hours of treatment, pregnancy)

Any treatments administered to manage adverse event:

Patient currently recovered: Yes/No/Unknown	**Do you think that the treatment was a possible cause of the adverse event?** Yes/No **If Yes, which drug do you think was responsible?**
Reporter's name and contact details:	**Signature and date:**

Notes

1. Send copies of this form to your District Medical Officer or Ministry of Health, the National Drug Regulatory Authority, the National Pharmacovigilance Centre and local WHO office.
2. Conceal the patient's name and forward scanned copies within one working day via email to pctdata@who.int and concerned relevant manufacturers as shown below:

Mectizan® Donation Program 325 Swanton Way, Decatur, GA30030	Fax number: Email:	**+1-404-393-9042** mectizan@mectizan.org
Merck Global Safety	Fax number: Email:	**+1-215-661-6229**
GlaxoSmithKline UK Case Management Group	Fax number: Email:	**+44 208 754 7821** UKCMG@gsk.com
Johnson & Johnson	Fax number: Email:	
Pfizer	Fax number: Email:	
Eisai Co., Ltd, Global Pharmacovigilance	Fax number: Email:	**+81-3-3811-2710** Eisai-asia_safety@hhc.eisai.co.jp
Merck KGaA, Global Drug Safety	Fax number: Email:	**+49 6151 726914** gds@merckgroup.com

Annex 2: Agreement for the application of Mectizan® donation for the elimination of LF

In applying for donated Mectizan® for mass distribution in association with Alb (donated by GSK) and DEC (donated by EISAI) for the elimination of lymphatic filariasis, the applicant agrees to:

1. Submit an elimination strategic plan and annual plan to inform on the country's elimination target (with an appropriate target year) and drug needs to guide adequate production and supply of the medicines
2. If required, register the donated Mectizan® with the relevant national regulatory authorities
3. Assure free entry of Mectizan® into the country without imposing duty, tax, or other cost
4. Upon receipt of the consignments, send the signed and stamped acknowledgment of receipt back to the Mectizan Donation Program (mectizan@mectizan.org)
5. Ensure the provision of in-country resources to implement the IDA including the storage of the medicines in the central warehouse, their transport to all the distribution points and their directly observed administration to the beneficiary population
6. Inform hospital/dispensary personnel, community leaders, and the beneficiary population about:
   a) what Mectizan® in association with Alb and DEC will NOT do (e.g. cure elephantiasis)
   b) the need for each treatment round to reach effective coverages
   c) possible IDA-related adverse events associated with IDA treatment
7. Ensure that correct procedures are applied during the distribution of Mectizan® in association with Alb and DEC, namely that:
   a) The following table is used to dose Mectizan for administration to eligible individuals (either height or weight may be used);

Weight Range (kg)	Number of 3 mg Mectizan Tablets	Height Range (cm)
15-25	1	90-119
26-44	2	120-140
45-64	3	141-158
65 or more	4	159 or more

b) Directly Observed Therapy (DOTs): Each person treated is observed to actually swallow the correct number combination of tablets

c) The following persons do **NOT** receive treatment:

- **o** children weighing less than 15 kg or who are less than 90 cm tall
- o pregnant women
- o women breast-feeding infants less than one week old
- o individuals with active serious illnesses of an acute or chronic nature
- o individuals with history of hypersensitivity response to a component of IDA

d) Arrangements are made to ensure eligible people who are not treated at this visit receive treatment later

e) Adequate records of the patients treated are maintained

f) Appropriate monitoring and surveillance for IDA-related adverse events (AE) is implemented in communities following mass drug administration

g) Health personnel are trained to manage any cases of IDA-related adverse events that may occur following mass drug administration

h) Health facilities and equipment are adequate to ensure the appropriate management of any cases without cost to the patient of IDA-related adverse events that may occur following mass drug administration

i) A Severe Adverse Event (SAE) Report is completed and submitted to the Mectizan Donation Program (mectizan@mectizan.org) for every patient who is identified as having had an IDA-related adverse event possibly associated with IDA

j) Any expired tablets should be incinerated

k) An Inventory Report of Mectizan® received to MDP (mectizan@mectizan.org) is submitted on an annual basis

l) An annual report is submitted to WHO—with copy to MDP—detailing treatments administered and epidemiological and parasitological data, as required by WHO.

Agreed to on behalf of the applicant institution by:

Signature of National Coordinator

Name (Please print or type)

Date (Day, Month, Year)

Signature of Minister of Health or Designee

Name (Please print or type)

Title

Address

City Province/State

Country

Telephone number Fax number

E-Mail

Date (Day, Month, Year)

Annex 3: Mectizan® Application for IDA: Mectizan Expert Committee (MEC) Review Form

MECTIZAN DONATION PROGRAM

Review of Mectizan® Application to accelerate LFE in countries where onchocerciasis is <u>not</u> endemic

Application #:	Country:
Applicant:	
Proposed start date:	
Reviewer: _____	

CRITICAL ELEMENT

1. Epidemiological eligibility of the implementation units targeted for IDA

Epidemiological eligibility[4]	Number of IUs	Name of IUs	Total population
a) IU that have not started (Priority 2)			
b) IU < 4 effective rounds of DA (Priority 2)			
c) IU that have not met the appropriate epidemiological targets in sentinel and spot-check site surveys or in TAS despite meeting drug coverage targets (Priority 1)			
d) for communities where post-MDA or post-validation surveillance identified infection suggesting local transmission (Priority 1)			
Total			

[4] Priority to be given to criteria c and d

2. Political commitment by country applying for Mectizan® for IDA

Criteria	Satisfactory	Unsatisfactory	Unable to Judge
Revised LF elimination master plan with new elimination target			
Adoption of IDA as a strategy to accelerate LFE			
If not registered, Government accepts the entry and use of Mectizan in the country for IDA under Special Access Scheme			
Government accepts free entry of Mectizan into the country without imposing duty, tax, or other costs			
Signed agreement			

3. Ability to plan and successfully implement an effective IDA

Criteria	Satisfactory	Unsatisfactory	Unable to Judge
Strong commitment of funding partner			
History of MDA with high coverage			
Planning of activities with potential to increase coverage			
- Training of health workers and drug distributors on IDA strategy			
- Strong social mobilization			
- Incentives for drug distributors (if applicable)			
Safety and AE preparedness, monitoring, management, and reporting			

4. Post MDA M&E impact assessment (for re-application for the THIRD ROUND)

	Number	List
UIs under IDA		
Coverage quality assessment		
- IUs with coverage > 70%		
- IUs with coverage < 70%		
Impact Assessment		
- Passed Pre-TAS		
- Passed TAS		

ADDITIONAL COMMENTS:

YOUR QUESTIONS FOR THE APPLICANT:

RECOMMENDATION (check only one)**:**

☐ Approve

☐ Disapprove

☐ Conditional Approval
please specify conditions:

SIGNATURE: _____ **DATE**: _____

Annex 4. Summary of Product Characteristics

1. Denomination

MECTIZAN® 3 mg tablets

2. Qualitative and Quantitative Composition

Each tablet of 60.00 mg contains:

Ivermectin	*3.000 mg*
Microcrystalline cellulose	*47.500 mg*
Pregelatinized corn starch	*9.000 mg*
Butylated hydroxanisole	*0.012 mg*
Citric acid anhydrous	*0.012 mg*
Magnesium stearate	*0.500 mg*

3. Pharmaceutical Form

tablet

4. Clinical Data

4.1. Indications

- for the treatment of onchocerciasis caused by *Onchocerca volvulus**.***
- for the treatment of proven or suspected microfilaremia in patients with lymphatic filariasis caused by *Wuchereria bancrofti or Brugia malayi.*

4.2. Dosage and administration

Treatment of onchocerciasis:

The recommended dosage of ivermectin in the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 µg/kg of body weight.

For the treatment of individual patients, retreatment may be considered after a 3-month interval.

In mass distribution campaigns for onchocerciasis, the most commonly used dose interval is 12 months. However, in some areas it may be preferable to repeat the administration every 6 months according to the prevalence or the cutaneous microfilarial density.

For your guidance, the dose as determined by the patient's weight is as follows:

Bodyweight (kg)	Number of 3 mg tablets
15 to 25	one
26 to 44	two
45 to 64	three
65 to 84	four

Alternatively, and if no scales are available, the dose of ivermectin for use in mass chemotherapy campaigns may be determined by the patient's height, as follows:

Height (cm)	Number of 3 mg tablets
90 to 119	one
120 to 140	two
141 to 158	three
> 158	four

Treatment of microfilaremia caused by *Wuchereria bancrofti:*

The recommended dosage for mass distribution for the treatment of microfilaremia caused by *Wuchereria bancrofti or Brugia malayi* is a single oral dose once every 12 months designed to provide approximately 150 to 200 µg/kg of body weight.

For your guidance, the dose, as determined by the patient's weight or height (in mass chemotherapy campaigns), is as follows:

Bodyweight (kg)	Number of 3 mg tablets	Height (cm)
15 to 25	one	90 to 119
26 to 44	two	120 to 140
45 to 64	three	141 to 158
65 to 84	four	> 158

Method of administration:

- Oral route
- In children less than 6 years of age, tablets should be crushed before swallowing
- Treatment is one single oral dose taken with water on an empty stomach
- The dosage may be taken at any time of the day, but no food should be taken within two hours before or after administration, as the influence of food on absorption is unknown

4.3. Contraindication

Hypersensitivity to any component of this product.

4.4. Warnings and particular precautions for use

Warnings

Ivermectin has no macrofilaricidal effect against adult forms of *Onchocerca volvulus* parasites, nor against other adult filarial parasites.

Ivermectin is not a prophylactic therapy of infection with filarial parasites. There are no data available demonstrating the efficacy of ivermectin either for killing or preventing the maturation of infective larvae in humans.

Ivermectin has not been shown to have any beneficial effect on tropical pulmonary eosinophilia syndrome, lymphadenitis or lymphangitis observed in case of infection with filarial parasites.

The intensity and severity of adverse experiences, after administration of ivermectin, are probably related to the pretreatment microfilarial density, particularly in the blood. Patients with high microfilaremia of *Loa loa* are at an increased risk for the occurrence of serious adverse experiences after administration of ivermectin. CNS adverse experiences (encephalopathies) have been rarely reported in patients treated with ivermectin and infected by a high number of microfilariae of *Loa loa*. Consequently, in *Loa loa* endemic areas, special measures should be taken before any treatment with ivermectin.

Concomitant treatment with DEC and ivermectin in mass chemotherapy campaigns for filariasis caused by *Wuchereria bancrofti* in Africa where onchocerciasis is endemic is not recommended. Both Ivermectin and DEC treatment of patients with Loa loa co-infection may result in the occurrence of serious side effects related to the rapid and effective microfilaricidal effects of these drugs.

Following administration of drugs with a rapid microfilaricidal action such as diethylcarbamazine citrate (DEC) in patients with onchocerciasis, cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmological reactions have been reported. These reactions are probably due to inflammatory responses to degradation products released following the death of microfilariae. Patients infected with *Onchocerca volvulus* who are treated with ivermectin for the first time may also experience these reactions. After treatment with a microfilaricidal drug, patients with hyperreactive onchodermatitis or "Sowda" (observed particularly in Yemen) may be more likely than others to experience severe cutaneous adverse reactions (edema and aggravation of onchodermatitis).

Precautions for use

Safety and effectiveness in pediatric patients weighing less than 15 kg have not been established.

4.5. Pregnancy and nursing

Pregnancy

After administration of repeated doses of ivermectin close to or equal to maternotoxic doses, fetal abnormalities have been observed in several animal species in the laboratory. From these studies, it is difficult to assess the risk of a single low dose.

In clinical studies no malformations or fetotoxic effects have been attributed to ivermectin. The frequencies of congenital anomalies, spontaneous abortions, fetal deaths/stillbirths and infant mortalities in approximately 400 women inadvertently treated with ivermectin during the first trimester of pregnancy in mass treatment campaigns for onchocerciasis were similar to frequencies in women not treated with ivermectin during pregnancy. However, follow-up of pregnancies of women exposed to ivermectin is not sufficient to exclude any risk. Therefore, as a precaution, it is advisable not to use ivermectin during pregnancy.

Nursing

Less than 2% of the administered dose of ivermectin appeared in breast milk.

Safety in newborn infants has not been established; therefore, the drug should be given to nursing mothers only if the benefit to the mother outweighs the potential risk to the breast-fed infant, and treatment of mothers who intend to breast feed their infants should be delayed until 1 week after birth of the child.

4.6. Side effects

Side effects are related to the microfilarial density; most of them are mild and transient in nature but the incidence and severity may be higher in patients infected with more than one parasite, as in the case of infection with *Loa loa*.

- Following treatment of patients infected with *Onchocerca volvulus* with ivermectin, the following hypersensitivity reactions may occur due to the death of microfilariae; these are symptoms of Mazzotti type reaction: pruritus, frank urticarial rash, conjunctivitis, arthralgia, myalgia (including abdominal myalgia), fever, edema, lymphadenitis, lymphadenopathies, nausea, vomiting, diarrhea, orthostatic hypotension, vertigo, tachycardia, asthenia, headache**.** These symptoms have been rarely severe. Some cases of worsening of bronchial asthma have been reported.

- Less frequently, ophthalmological side effects after treatment with ivermectin may occur. These include: abnormal sensation in the eyes, eyelid edema, anterior uveitis, conjunctivitis, limbitis, keratitis and chorioretinitis or chorioditis. All of these can occur due to the disease itself but have occasionally been reported after therapy. These have rarely been severe and have generally resolved without corticosteroid treatment.

- In the treatment of filariasis caused by *Wuchereria bancrofti*, the intensity of the side effects does not seem to be dose-related but is related to the blood microfilarial density. The following have been reported: fever, headache, asthenia, feeling of weakness, myalgia, arthralgia, body pain, digestive disorders such as anorexia, nausea, abdominal and epigastric pain, cough, feeling of respiratory discomfort, postural hypotension, chills, vertigo, diaphoresis, sore throat, testicular pain or discomfort.

- Very rarely, patients who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy following treatment with ivermectin.

- Transient hypereosinophilia, liver function abnormalities (SGPT) and hematuria have been reported.

- Cases of expulsion of adult ascaris worms have been described following administration of ivermectin.

4.7. Overdosage

There are reports of accidental overdosage of ivermectin, but no fatalities have been attributable to ivermectin overdosing.

In accidental intoxication with unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection or exposure to body surfaces, the following symptoms have been reported: rash, edema, headache, vertigo, asthenia, nausea, vomiting, diarrhea, abdominal pain. Other adverse effects that have been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, and urticaria.

Management in case of accidental poisoning:
- supportive therapy and supervision in specialized care unit with fluid replacement, and treatment for hypotension, if needed.

Although there are no data available in man, it seems advisable to avoid the use of GABA agonists in the treatment of accidental intoxications due to ivermectin.

5. Pharmacological Properties

5.1. Pharmacodynamics

Anthelmintic

Ivermectin is derived from the avermectins, that are isolated from fermentation broths of *Streptomyces avermitilis*. It binds selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite.

Ivermectin may also interact with other lingand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

Mammals do not have glutamate-gated chloride channels. The avermectins have a low affinity for mammalian ligand-gated chloride channels. They do not readily cross the blood-brain barrier in humans.

In patients infected with *Onchocerca volvulus*, a single oral dose of 150 µg/kg ivermectin resulted in a decrease in the number of skin microfilariae to undetectable levels within a few days. This reduction was maintained at or under 10% of the pre-treatment microfilarial count for up to 12 months after treatment. This effect is due to the microfilaricidal effect and to the transient blockage of the release of microfilariae from the uterus of the adult worm. As with other microfilaricidal drugs, there was an increase in the microfilariae count in the anterior chamber of the eye at day 3 after treatment in some patients. However, at 3

and 6 months after the dose, a significant reduction in the number of microfilariae in the anterior chamber of the eye was observed in subjects treated.

Clinical studies conducted in Africa, Asia, South America, the Caribbean, and Polynesia in patients with microfilaremia caused by *Wuchereria bancrofti* demonstrated that a single oral dose of at least 100 µg/kg ivermectin resulted in reduction of microfilaremia to below 1% of the pre-treatment
value in the week following administration. These studies showed that the treatment effect was dose-dependent with regard to the duration of the reduction in microfilaremia and the prevalence

in the population treated. The use of ivermectin in mass treatment of populations for the treatment of microfilaremia in man, the unique host for *Wuchereria bancrofti*, may be useful to decrease the transmission of *Wuchereria bancrofti* by vector insects, thus interrupting the infectious cycle of the disease.

5.2. Pharmacokinetics

With 12 mg single oral doses of MECTIZAN administered as tablets, the mean peak plasma concentration of the major component (H_2B_1a) was 46.6 (± 21.9) ng/ml at approximately 4 hours after dosing. Plasma concentration increases with increasing dose in a manner approximately proportional to the dose. Ivermectin is metabolized in humans, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 hours less than 1% of the administered dose being excreted in the urine. The plasma half-life of ivermectin in man is about 12 hours and that of the metabolites is about 3 days.

6. Pharmaceutical Data

6.1. Stability

3 years

6.2. Special precautions for storage

Do not store above 30°C.

6.3. Nature and content of the packaging

500 tablets in bottle (PE)

7. Presentations and Administrative Identification Numbers
500 tablets in bottle (PE)
A.M.M. (ANSM-France): 343 368.5 14/05/1997

8. Prescription and Delivery Conditions

List II

9. A.M.M. HOLDER

Merck Sharp & Dohme BV
Waarderweg 39,
2031 BN Haarlem
PAYS-BAS
or
Laboratoires Merck Sharp & Dohme-Chibret
Route de Marsat
63200 Riom-France

10. Approval/Revision Dates
Approval date: 14.05.97
Revision date: 14.05.07