CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-742/S-001

APPROVED LABELING
STROMECTOL® (ivermectin)

**SEP 2 9 2000**

**STROMECTOL® (Ivermectin)** is a semisynthetic, anthelmintic agent for oral administration. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum endectocides isolated from the fermentation products of Streptomyces avermitilis. Ivermectin is a mixture containing at least 90% 5-O-demethyl-22,23-dihydroivermectin A₁b and less than 10% 5-O-demethyl-23-de-1-methylpropyl-22,23-dihydro-25-t-methylthiethylavermectin A₁b; generally referred to as 22,23-dihydroivermectin B₁b and B₂b, or H₂B₁b and H₂B₂b, respectively. The respective empirical formulas are C₂₄H₃₈O₈ and C₂₄H₃₈O₈, with molecular weights of 875.10 and 861.07, respectively. The structural formulas are:

Component B₁b, R = C₂H₅
Component B₂b, R = CH₃

Ivermectin is a white to yellowish-white, nonhygroscopic, crystalline powder with a melting point of about 155°C. It is insoluble in water but is freely soluble in methanol and soluble in 95% ethanol.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose. In two studies, after single 12-mlg doses of STROMECTOL® (2.6 mg) in fasting healthy volunteers (representing a mean dose of 165 µg/kg), the mean peak plasma concentrations of the major component (A₁b) were 4.6 ± 2 (1.1) (range: 16.4 ± 10.1) and 30.6 ± 15.6 (range: 13.3 ± 6.4) ng/mL respectively at approximately 4 hours after dosing. Ivermectin is metabolized in the liver, and ivermectin and its metabolites are excreted almost exclusively in the urine over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. The apparent plasma half-life of ivermectin is approximately at least 15 hours following oral administration.

**Microbiology**

Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents which have a unique mode of action. Compounds of the class bind 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. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The selective activity of compounds of this class is attributable to the fact that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels. In addition, ivermectin does not readily cross the blood-brain barrier in humans. Ivermectin is active against various life cycle stages of many but not all nematodes. It is active against the tissue microfilariae of Onchocerca volvulus but not against the adult form. Its activity against Strongyloides stercoralis is limited to the intestinal stages.

**Clinical Studies**

**Strongyloides**

Two controlled clinical studies using abendazole as the comparative agent were carried out in international sites where abendazole is approved for the treatment of Strongyloides of the gastrointestinal tract, and three controlled comparative studies. Efficacy, as measured by cure rate, was defined as the absence of larvae in at least two follow-up stool examinations 3104 weeks post therapy. Based on this criterion, ivermectin was significantly greater for STROMECTOL® (single dose of 170 to 200 µg/kg) than abendazole (200 mg bid for 3 days). STROMECTOL administered as a single dose of 200 µg/kg for

<table>
<thead>
<tr>
<th>Curing Rate (%)</th>
<th>Ivermectin</th>
<th>Comparative Agent</th>
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<tbody>
<tr>
<td>WHO Study</td>
<td>12/20 (55)</td>
<td>6/20 (30)</td>
</tr>
<tr>
<td>US Studies</td>
<td>13/15 (97)</td>
<td>6/10 (45)</td>
</tr>
</tbody>
</table>

In one study conducted in France, a non-endemic area where there was no possibility of reinfection, several patients were observed to be free of Strongyloides larvae in their stool as long as 106 days following treatment. Therefore, at least three stool examinations should be conducted over the three months following treatment to ensure eradication. If recurrence of larvae is observed, retreatment with ivermectin is indicated. Concentration techniques (such as using a Baermann apparatus) should be employed when performing these stool examinations, as the number of Strongyloides larvae per gram of feces may be very low.

**Onchocerciasis**

The efficacy of STROMECTOL in the treatment of onchocerciasis is based on the results of clinical studies involving 1278 patients. In a double-blind, placebo-controlled study involving patients with moderate to severe onchocercal infection, patients who received a single dose of 150 µg/kg STROMECTOL experienced a 83.2% and 95.6% decrease in skin microfilarial count (geometric mean) 3 days and 3 months after the dose, respectively. A marked reduction of > 50% was maintained for up to 12 months after the single dose. As with other microfilaricidal drugs, there was an increase in the microfilarial count in the anterior chamber of the eye of 6-15% 3 months after treatment in some patients. However, at 3 and 6 months after the dose, a significantly greater percentage of patients treated with STROMECTOL had decreases in microfilarial count in the anterior chamber than patients treated with placebo.

In a separate open study involving pediatric patients ages 6 to 13 (n=103; weight range: 17-41 kg), similar decreases in skin microfilarial counts were observed for up to 12 months after dosing.

**INDICATIONS AND USAGE**

STROMECTOL is indicated for the treatment of the following infections:

- **Strongyloides of the intestinal tract.** STROMECTOL is indicated for the treatment of intestinal (i.e., non-disseminated) strongyloidiasis due to the nematode parasite *Strongyloides stercoralis*.

This indication is based on randomized, double-blind, placebo-controlled and comparative studies conducted in 1427 patients in onchocerciasis-endemic areas of West Africa. The comparative studies used diethylcarbamazine citrate (DEC-C).

**NOTE:** STROMECTOL has no activity against adult *Onchocerca volvulus* parasites. The adult parasites are found in subcutaneous nodules which are frequently palpable. Surgical excision of these nodules (nodulotomy) may be considered in the management of patients with onchocerciasis, since this procedure will eliminate the microfilariae-producing adult parasites.

**CONTRAINDICATIONS**

STROMECTOL is contraindicated in patients who are hypersensitive to any component of this product.

**WARNINGS**

Historical data have shown that microfilaricidal drugs, such as diethylcarbamazine citrate (DEC-C), might cause cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmological reactions in patients with onchocerciasis. These reactions are probably due to allergic and inflammatory responses to the death of microfilariae. Patients treated with STROMECTOL for onchocerciasis may experience these reactions in addition to clinical adverse reactions possibly, probably, or definitely related to the drug itself. (See ADVERSE REACTIONS, Onchocerciasis.)

The treatment of severe Mazzotti reactions has not been subjected to controlled clinical trials. Oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat postural hypotension. Antihistamines and/or aspirin have been used for most mild to moderate cases.

**PRECAUTIONS**

**General**

After treatment with microfilaricidal drugs, patients with hyperreactive onchodermatitis (swelling) may be more likely than others to experience severe adverse reactions, especially edema and aggravation of onchodermatitis.

**Archontogogy**

Molluscan, Molluscicidal effects were not significantly greater for STROMECTOL than for placebo in mice infected with *S. mansoni*.
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LS178Y (cytotoxicity and mutagenicity) assays, or the unscheduled DNA synthesis assay, all human fibroblasts.

Ivermectin had no adverse effects on the fertility in rats as studies at repeated doses of up to 3 times the maximum recommended human dose of 200 μg/kg (on a mg/kg/day basis).

Information for Patients

STROMECTOL should be taken with water.

Strongyloidiasis: The patient should be reminded of the need for repeated stool examinations to document clearance of infection with Strongyloides stercoralis. 

Onchocerciasis: The patient should be reminded that treatment with STROMECTOL does not kill the adult Onchocerca parasites, and therefore repeated follow-up and retreatment is usually required.

Pregnancy, Teratogenic Effects

Pregnancy Category C

Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8, and 4.5 times the maximum recommended human dose, respectively (on a mg/kg/day basis). Teratogenicity was characterized in the three species tested by cleft palate, clubbed forepaws were additionally observed in rabbits. These development effects were found only at or near doses that were maternal toxic to the pregnant female. Therefore, ivermectin does not appear to be selectively toxic to the developing fetus. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.

Nursing Mothers

STROMECTOL is excreted in human milk in low concentrations. Treatment of mothers who intend to breast feed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.

Pediatrics

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

Strongyloidiasis in Immunocompromised Hosts

In immunocompromised (including HIV-infected) patients being treated for intestinal strongyloidiasis, repeated courses of therapy may be required. Adequate and well-controlled clinical studies have not been conducted in such patients to determine the minimal duration of treatment, i.e., at least weekly intervals, may be required, and cure may not be achievable. Control of extra-intestinal strongyloidiasis in these patients is difficult, and suppressive therapy, i.e., once per month may be helpful.

ADVERSE REACTIONS

Strongyloidiasis

In four clinical studies involving a total of 109 patients given either one or two doses of 170 to 200 μg/kg of STROMECTOL, the following adverse reactions were reported as possibly, probably, or definitely related to STROMECTOL:

- Body as a whole: asthenia/fatigue (0.3%), abdominal pain (0.9%)
- Gastrointestinal: anorexia (0.9%), constipation (0.9%), diarrhea (1.8%), nausea (1.8%), vomiting (0.9%)
- Nervous System/Psychiatric: dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), tremor (0.9%)
- Skin: pruritus (2.8%), rash (0.9%), and urticaria (0.9%)

In comparative trials, patients treated with STROMECTOL experienced more abdominal distention and chest discomfort than patients treated with albendazole. However, STROMECTOL was better tolerated than thiabendazole in comparative studies involving 37 patients treated with thiabendazole.

The Mazotti-type and ophthalmologic reactions associated with the treatment of onchocerciasis or the disease itself would not be expected to occur in strongyloidiasis patients treated with STROMECTOL. (See ADVERSE REACTIONS, Onchocerciasis.)

Laboratory Test Findings

In clinical trials involving 109 patients given either one or two doses of 170 to 200 μg/kg of STROMECTOL, the following laboratory abnormalities were seen irrespective of drug relationship: elevation in ALT and/or AST (2%), decrease in leukocyte count (3%). Leukopenia and anemia were seen in one patient.

Onchocerciasis

In clinical trials involving 963 adult patients treated with 100 to 200 μg/kg STROMECTOL, worsening of the following Mazotti reactions during the first 4 days post-treatment were reported: rhinorrhea/serositis (9.3%), axillary lymph node enlargement and tenderness (11.0% and 4.4%, respectively), cervical lymph node enlargement and tenderness (5.3% and 1.2%, respectively), inguinal lymph node enlargement and tenderness (12.6% and 13.9%, respectively), oropharyngeal and tonsillitis (2.0% and 1.9%, respectively), pruritus (27.5%), skin involvement including edema, papular and pustular or frank urticarial rash (22.7%), and fever (22.6%). (See WARNINGS.)

In clinical trials, ophthalmologic examinations were examined in 963 adult patients before treatment, at day 3, and months 3 and 6 after treatment with 100 to 200 μg/kg STROMECTOL. Changes observed were primarily deterioration from baseline 3 days post-treatment. Mean changes either returned to baseline condition or improved over baseline severity at the month 3 and 6 visit. The percentage of patients with worsening of the following conditions at day 3, month 3 and 6, respectively, were: limbitis 5.5%, 4.3%, and 3.5% and punctate opacity: 1.8%, 1.8%, and 1.4%. The corresponding percentages for patients treated with placebo were: limbitis 8.7%, 13.5%, and 9.4% and punctate opacity 2.0%, 6.4%, and 7.2%. (See WARNINGS.)

In clinical trials involving 963 adult patients who received 100 to 200 μg/kg STROMECTOL, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in 5% of the patients: facial edema (1.2%), peripheral edema (3.2%), orthostatic hypotension (1.1%), and tachycardia (3.6%). Drug-related headache and myalgia occurred in <1% of patients (0.2% and 0.1%, respectively). However, no unusual adverse experiences reported overall during these trials regardless of causality (22.3% and 19.7%, respectively).

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A similar safety profile was observed in an open study in pediatric patients 5 to 12 years old. Additional, hypotension (mainly orthostatic hypotension) and worsening of bronchial asthma have been reported since the drug was registered overseas. The following ophthalmologic side effects do occur due to the disease itself but have also been reported after treatment with STROMECTOL: abnormal sensation in the eyes, eyelid edema, anterior uveitis, conjunctivitis, limbal, keratitis, and chorioretinitis pr. choroideits. These have rarely been severe or associated with loss of vision and have generally resolved without corticosteroid treatment.

Laboratory Test Findings

In controlled clinical trials, the following laboratory adverse experiences were reported as possibly, probably, or definitely related to the drug in 2% of the patients: eosinophilia (3%) and hemoglobin increase (1%).

OVERDOSAGE

Significant lethality was observed in mice and rats after single oral doses of 25 to 50 mg/kg and 40 to 50 mg/kg, respectively. No significant lethality was observed in dogs after single oral doses of up to 10 mg/kg. At these doses, the treatment related signs that were observed in these animals included ataxia, tremors, ptosis, decreased activity, anemia, and mydriasis.

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

In case of accidental poisoning, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary) and pressor agents if clinically significant hypotension is present. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine anti-poison measures, may be indicated if needed to prevent absorption of ingested material.

DOSAGE AND ADMINISTRATION

Strongyloidiasis

The recommended dosage of STROMECTOL for the treatment of strongyloidiasis is a single oral dose designed to provide approximately 200 μg of ivermectin per kg of body weight. See Table 1 for dosage guidelines. Patients should take tablets with water. In general, additional doses are not necessary. However, follow-up stool examinations should be performed to verify eradication of infection (see Clinical Studies.)

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Single Oral Dose</th>
<th>Number of 200 μg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>1 tablet</td>
<td>5 tablet</td>
</tr>
<tr>
<td>25-35</td>
<td>2 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>36-50</td>
<td>3 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>51-65</td>
<td>4 tablets</td>
<td>2 tablets</td>
</tr>
<tr>
<td>66-79</td>
<td>5 tablets</td>
<td>2 tablets</td>
</tr>
<tr>
<td>80</td>
<td>2 tablets</td>
<td>2 tablets</td>
</tr>
<tr>
<td>200 μg/kg</td>
<td>2 tablets</td>
<td>2 tablets</td>
</tr>
<tr>
<td>200 μg/kg</td>
<td>2 tablets</td>
<td>2 tablets</td>
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</tbody>
</table>

Onchocerciasis

The recommended dosage of STROMECTOL for the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 μg of ivermectin per kg of body weight. See Table 2 for dosage guidelines. Patients should take tablets with water. In mass distribution campaigns in international treatment programs, the most commonly used dose interval is 12 months. For the treatment of individual patients, retreatment may be considered at intervals as short as 3 months.

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Single Oral Dose</th>
<th>Number of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-25</td>
<td>1 tablet</td>
<td>1 tablet</td>
</tr>
<tr>
<td>26-44</td>
<td>2 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>45-64</td>
<td>3 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>65-84</td>
<td>4 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>85-105</td>
<td>150 μg/kg</td>
<td>1 tablet</td>
</tr>
<tr>
<td>105 μg/kg</td>
<td>150 μg/kg</td>
<td>1 tablet</td>
</tr>
</tbody>
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HOW SUPPLIED

No. 8107 — Tablets STROMECTOL 6 mg are white, scored, round, flat, bevel-edged tablets coded MSD 139 on one side and branded on the other. They are supplied as follows:

No. 8107: 100 unit dose packages of 10.
No. 8495 — Tablets STROMECTOL 3 mg are white, round, flat, bevel-edged tablets coded MSD on one side and 32 on the other side. They are supplied as follows:

NDC 0006-0032-20 unit dose packages of 20.

Storage

Store at temperatures below 30°C (86°F).

MERCK & CO., INC., West Point, PA 19486, USA

Manufactured by: MSD BV

Waardenweg 29

2531 BN Laarne

Netherlands

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