[Norman Schmuff, Ph.D. Chem. Team Leader, DNDC III. (Oct. 08, 1998). Drug Approval Package to Merck & Co., Inc., Frank Ricci, approving Stromectol (Ivermectin) Tablets, 6 mg, then 3 mg., App. No. 050742s001, Dec. 12, 1997. U.S. FDA. Center for Drug Evaluation and Research. Sources: https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/50-742s001_Stromectol_Approv.PDF | https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/50-742s001_Stromectol.cfm]

NDA 50-742/S-001

OCT 8 1998

Merck & Co., Inc.
Attention: Frank Ricci
Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486

OCT 8 1998

Dear Mr. Ricci:

Reference is made to your supplemental New Drug Application dated December 12, 1997, submitted pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for Stromectol® (Ivermectin) Tablets, 6 mg. Reference is also made to your amendment dated October 7, 1998.

This supplemental application provides for a new tablet strength (3 mg).

We have completed the review of this supplemental application, as amended, and it is approved, effective on the date of this letter.

We remind you that you must comply with requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

/S/

Norman Schmuff, Ph.D.
Chemistry Team Leader, DNDC III
Division of Special Pathogen and Immunologic
Drug Products (HFD-590)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Distribution:
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HFD-590/CSO
HFD-830/CChen
HFR-/Field

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-742 / S-001

APPROVAL LETTER

FDA U.S. FOOD & DRUG ADMINISTRATION

Drug Approval Package

Stromectol (Ivermectin) Tablets
Company: Merck & Co., Inc.
Application No.: 050742s001
Approval Date: 10/08/1998

- Approval Letter(s) (PDF)
- Approvable Letter(s) (PDF)
- Printed Labeling (PDF)
- Chemistry Review(s) (PDF)
- Administrative Document(s) & Correspondence (PDF)

Date created: March 3, 2005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-742 / S-001

APPROVABLE LETTER

DIV

NDA 50-742/S-001

JUN 15 1998

Merck & Co., Inc.
Attention: Kenneth R. Brown, M.D.
Sumneytown Pike, P.O. Box 4
BLA-14B
West Point, PA 19468

Dear Dr. Brown:

Please refer to your supplemental new drug application dated December 12, 1997, received December 15, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stromectol® (Ivermectin) Tablets, 6 mg.

We acknowledge receipt of your submission dated December 12, 1997. The user fee goal date is June 15, 1998.

The supplemental application provides for a new tablet strength (3 mg.)

We have completed the review of this supplemental application and it is approvable. Before this supplement may be approved, however, it will be necessary for you to:

1. Please provide comparative dissolution data comparing the dissolution profiles of contemporaneous batches of 3-mg and 6-mg tablets.

2. Please provide all available room temperature and accelerated stability date for lots HE36950, HE36960, and HE37080.

3. Please revise the testing schedule for annual post-approval stability batches to 0, 3, 6, 9, 12, 18, and 24 months. A reduced testing schedule may be requested in a supplemental application when data to support it is obtained from stability studies of production batches.

4. Please explain the information on page 165 that appears to indicate that batch [redacted] was manufactured with sufficient ivermectin for each tablet to contain [redacted] of the drug substance, which would appear to be nearly [redacted] excess.

5. Please clarify what units are used to measure tablet hardness.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Mary Dempsey, Project Manager, at (301) 827-2127.

Sincerely yours,

/S/

Norman Schmuff, Ph.D.
Chemistry Team Leader, DNDC III
Division of Special Pathogen and Immunologic
Drug Products (HFD-590)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Distribution:
HFD-590 Orig. NDA
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APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-742/S-001

APPROVED LABELING

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

TABLETS

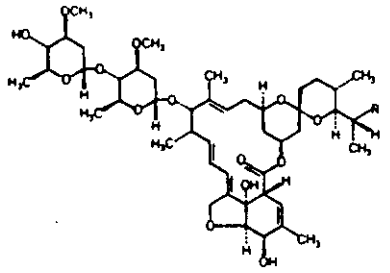
STROMECTOL®

SEP 2 9 2000

(IVERMECTIN)

DESCRIPTION

STROMECTOL® (Ivermectin) is a semisynthetic, anthelmintic agent for oral administration. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum anti-parasitic agents isolated from the fermentation products of *Streptomyces avermitilis*. Ivermectin is a mixture containing at least 90% 5-*O*-demethyl-22,23-dihydroavermectin A_{1a} and less than 10% 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectin A_{1a}, generally referred to as 22,23-dihydroavermectin B_{1a} and B_{1b}, or H_2B_{1a} and H_2B_{1b}, respectively. The respective empirical formulas are $C_{48}H_{74}O_{14}$ and $C_{47}H_{72}O_{14}$, with molecular weights of 875.10 and 861.07, respectively. The structural formulas are:



Component B_{1a}, R = C_2H_5 Component B_{1b}, R = CH_3

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.

STROMECTOL is available in 3-mg tablets and 6-mg scored tablets. Each tablet contains the following inactive ingredients: microcrystalline cellulose, pregelatinized starch, magnesium stearate, butylated hydroxyanisole, and citric acid powder (anhydrous).

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose. In two studies, after single 12-mg doses of STROMECTOL (2x6 mg) in fasting healthy volunteers (representing a mean dose of 165 µg/kg), the mean peak plasma concentrations of the major component (H_2B_{1a}) were 46.6 (±21.9) (range: 16.4-101.1) and 30.6 (±15.6) (range: 13.9-68.4) ng/mL respectively at approximately 4 hours after dosing. Ivermectin is metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the feces 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 16 hours following oral administration.

The effect(s) of food on the systemic availability of ivermectin has not been studied.

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 facts 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

Strongyloidiasis

Two controlled clinical studies using albendazole as the comparative agent were carried out in international sites where albendazole is approved for the treatment of strongyloidiasis of the gastrointestinal tract, and three controlled studies were carried out in the US and internationally using thiabendazole as the comparative agent. Efficacy, as measured by cure rate, was defined as the absence of larvae in at least two follow-up stool examinations 3 to 4 weeks post-therapy. Based on this criterion, efficacy was significantly greater for STROMECTOL (a single dose of 170 to 200 µg/kg) than for albendazole (200 mg b.i.d. for 3 days). STROMECTOL administered as a single dose of 200 µg/kg for 1 day was as efficacious as thiabendazole administered at 25 mg/kg b.i.d. for 3 days.

Summary of Cure Rates for Ivermectin Versus Comparative Agents in the Treatment of Strongyloidiasis

	Cure Rate* (%)	
	Ivermectin**	Comparative Agent
Albendazole*** Comparative		
International Study	24/26 (92)	12/22 (55)
WHO Study	126/152 (83)	67/149 (45)
Thiabendazole† Comparative		
International Study	9/14 (64)	13/15 (87)
US Studies	14/14 (100)	16/17 (94)

* Number and % of evaluable patients
** 170-200 µg/kg
*** 200 mg b.i.d. for 3 days
† 25 mg/kg b.i.d. for 3 days

In one study conducted in France, a non-endemic area where there was no possibility of reinfection, several patients were observed to have recrudescence of *Strongyloides* larvae in their stool as long as 106 days following ivermectin therapy. Therefore, at least three stool examinations should be conducted over the three months following treatment to ensure eradication. If recrudescence 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 evaluation 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 adult patients with moderate to severe onchocercal infection, patients who received a single dose of 150 µg/kg STROMECTOL experienced an 83.2% and 99.5% decrease in skin microfilariae count (geometric mean) 3 days and 3 months after the dose, respectively. A marked reduction of >90% was maintained for up to 12 months after the single dose. 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 significantly greater percentage of patients treated with STROMECTOL had decreases in microfilariae 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 microfilariae counts were observed for up to 12 months after dosing.

INDICATIONS AND USAGE

STROMECTOL is indicated for the treatment of the following infections:

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

This indication is based on clinical studies of both comparative and open-label designs, in which from 64-100% of infected patients were cured following a single 200 µg/kg dose of ivermectin. (See *Clinical Studies*.)

Onchocerciasis. STROMECTOL is indicated for the treatment of onchocerciasis due to the nematode parasite *Onchocerca volvulus*.

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 reside in subcutaneous nodules which are infrequently palpable. Surgical excision of these nodules (nodulectomy) 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 (sowda) may be more likely than others to experience severe adverse reactions, especially edema and aggravation of onchodermatitis.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ivermectin.

Ivermectin was not genotoxic *in vitro* in the Ames microbial mutagenicity assay of *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without rat liver enzyme activation, the Mouse Lymphoma Cell Line

L5178Y (cytotoxicity and mutagenicity) assays, or the unscheduled DNA synthesis assay in human fibroblasts.

Ivermectin had no adverse effects on the fertility in rats in studies at repeated doses of up to 3 times the maximum recommended human dose of 200 µg/kg (on a mg/m²/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, 8.1, and 4.5 times the maximum recommended human dose, respectively (on a mg/m²/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 maternotoxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developjng 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.

Pediatric Use

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 optimal dosing regimen. Several treatments, i.e., at 2 week 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 (0.9%), 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 Mazzotti-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 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 Mazzotti reactions during the first 4 days post-treatment were reported: arthralgia/synovitis (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), other lymph node enlargement and tenderness (3.0% 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, ophthalmological conditions 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. Most changes either returned to baseline condition or improved over baseline severity at the month 3 and 6 visits. The percentages of patients with worsening of the following conditions at day 3, month 3 and 6, respectively, were: limbitis: 5.5%, 4.8%, and 3.5% and punctate opacity: 1.8%, 1.8%, and 1.4%. The corresponding percentages for patients treated with placebo were: limbitis: 6.2%, 9.9%, 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 ≥1% of the patients: facial edema (1.2%), peripheral edema (3.2%), orthostatic hypotension (1.1%), and tachycardia (3.5%). Drug-related headache and myalgia occurred in <1% of patients (0.2% and 0.4%, respectively). However, these were the most common adverse experiences reported overall during these trials regardless of causality (22.3% and 19.7%, respectively).

A similar safety profile was observed in an open study in pediatric patients ages 6 to 13.

Additionally, hypotension (mainly orthostatic hypotension) and worsening of bronchial asthma have been reported since the drug was registered overseas.

The following ophthalmological 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, limbitis, keratitis, and chorioretinitis or choroiditis. 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 ≥1% 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 include ataxia, bradypnea, tremors, ptosis, decreased activity, emesis, and mydriasis.

In accidental intoxication with or significant exposure to unknown 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: seizure, 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 1
Dosage Guidelines for STROMECTOL for Strongyloidiasis

Body Weight (kg)	Single Oral Dose	
	Number of 3-mg Tablets	Number of 6-mg Tablets
15-24	1 tablet	½ tablet
25-35	2 tablets	1 tablet
36-50	3 tablets	1½ tablets
51-65	4 tablets	2 tablets
66-79	5 tablets	2½ tablets
≥80	200 µg/kg	200 µg/kg

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 2
Dosage Guidelines for STROMECTOL for Onchocerciasis

Body Weight (kg)	Single Oral Dose	
	Number of 3-mg Tablets	Number of 6-mg Tablets
15-25	1 tablet	½ tablet
26-44	2 tablets	1 tablet
45-64	3 tablets	1½ tablet
65-84	4 tablets	2 tablets
≥85	150 µg/kg	150 µg/kg

HOW SUPPLIED

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

NDC 0006-0139-10 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).

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

Manufactured by:
MSD BV
Waarderweg 39
2031 BN Haarlem
Netherlands

Issued October 1998
Printed in the Netherlands

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-742 / S-001

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW # 1	1. ORGANIZATION HFD-590	2. NDA NUMBER 50-742

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Merck & Co., Inc.
West Point, PA 19468-0004

4. AF NUMBER

5. DOCUMENT(S)

NUMBERS	DATES
SCF-001	12/12/97

6. NAME OF DRUG
Stromectol® Tablets

7. NONPROPRIETARY NAME
Ivermectin

8. SUPPLEMENT(S) PROVIDES FOR:
A new tablet strength (3 mg).

9. AMENDMENTS AND OTHER DATES

10. PHARMACOLOGICAL CATEGORY
Anthelmintic

11. HOW DISPENSED
[X] Rx | | OTC

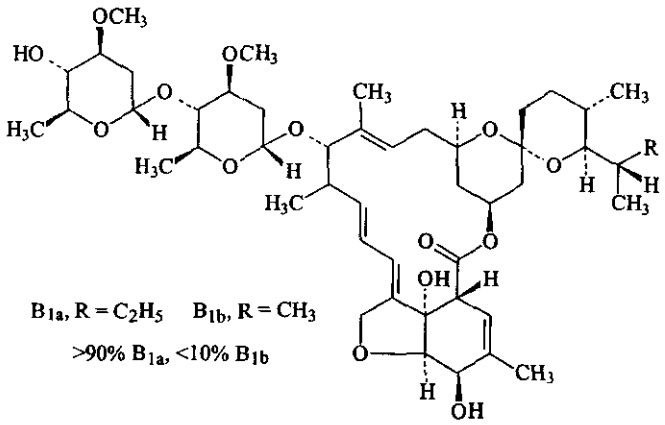
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM(S)
Tablet

14. POTENCY (CIES)
6 mg

15. CHEMICAL NAME
≥90% 5-*O*-demethyl-22,23-dihydroavermectin A_{1a} (A.K.A. 22,23-dihydroavermectin B_{1a}) and <10% 5-*O*-demethyl-25-de(1-methyl-propyl)-22,23-dihydro-25-(1-methylethyl) avermectin A_{1a} (A.K.A. 22,23-dihydroavermectin B_{1b})

$C_{48}H_{74}O_{14}$ & $C_{47}H_{72}O_{14}$ M.W. 875.10 & 861.07



B_{1a}, R = C_2H_5 B_{1b}, R = CH_3

>90% B_{1a}, <10% B_{1b}

16. MEMORANDA
N/A

17. COMMENTS
This supplemental application provides for a new tablet strength (3 mg).

In support of the new tablet strength, the applicant has provided descriptions of the composition, manufacturing process and controls, release and stability specifications, and analytical methods, and release test data on 6 lots and stability data on 3 lots.

Comparative dissolution data and some stability data was not provided.

18. CONCLUSIONS AND RECOMMENDATIONS
Forward comments to firm.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
John Smith		mm/dd/yy

20. CONCURRENCE: HFD-590/NSchmuff

DISTRIBUTION	X	Original Jacket	X	JSmith	X	MO
	X	Division File	X	NSchmuff	X	CSO
			X	HFD-830/CChen		

WITHHOLD 5 PAGE(S)

Exemption 4

SUPPLEMENTAL NDA CHEMIST'S REVIEW # 2	1. ORGANIZATION HFD-590	2. NDA NUMBER 50-742

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Merck & Co., Inc.
West Point, PA 19468-0004

4. AF NUMBER

5. DOCUMENT(S)

NUMBERS	DATES
SCF-001	12/12/97
AC	06/18/98

6. NAME OF DRUG
Stromectol® Tablets

7. NONPROPRIETARY NAME
Ivermectin

8. SUPPLEMENT(S) PROVIDES FOR:
A new tablet strength (3 mg).

9. AMENDMENTS AND OTHER DATES
10/07/98

10. PHARMACOLOGICAL CATEGORY
Anthelmintic

11. HOW DISPENSED
|X| R | | OTC

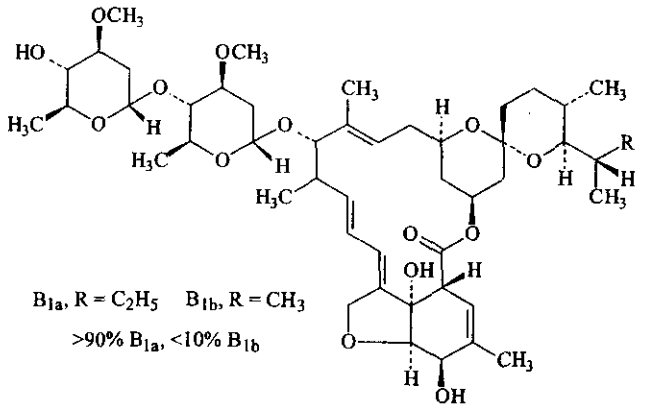
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM(S)
Tablet

14. POTENCY (CIES)
6 mg

15. CHEMICAL NAME
≥90% 5-*O*-demethyl-22,23-dihydroavermectin A_{1a} (A.K.A. 22,23-dihydroavermectin B_{1a}) and <10% 5-*O*-demethyl-25-de(1-methyl-propyl)-22,23-dihydro-25-(1-methylethyl) avermectin A_{1a} (A.K.A. 22,23-dihydroavermectin B_{1b})

$C_{48}H_{74}O_{14}$ & $C_{47}H_{72}O_{14}$ M.W. 875.10 & 861.07



B_{1a}, R = C_2H_5 B_{1b}, R = CH_3

>90% B_{1a}, <10% B_{1b}

16. MEMORANDA
N/A

17. COMMENTS
This supplemental application provides for a new tablet strength (3 mg).

In support of the new tablet strength, the applicant has provided descriptions of the composition, manufacturing process and controls, release and stability specifications, and analytical methods, and release test data on 6 lots and stability data on 3 lots. Comparative dissolution data was provided in the 06/18/98 amendment.

In response to our fax on 09/23/98, the reduced testing schedule for annual stability batches was removed in the 10/07/98 amendment.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: APPROVAL.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
John Smith		09/17/98 & 10/08/98

20. CONCURRENCE: HFD-590/NSchmuff

DISTRIBUTION	X	Original Jacket	X	JSmith	X	MO
	X	Division File	X	NSchmuff	X	CSO
			X	HFD-830/CChen		

WITHHOLD 4 PAGE(S)

Exemption 4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-742 / S-001

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

NDA 50-742/Final Printed Labeling

Labeling and Clinical Review of Final Printed Labeling:

Sponsor: Merck Research Laboratories

Product: Stromectol ™ (Ivermectin) 3 mg tablets (New Formulation)

Background:
NDA 50-742 (Stromectol ™ Tablets) 6 mg was originally approved for the treatment of strongyloidiasis of the intestinal tract and onchocerciasis on November 22, 1996. No labeling changes have been approved since the original approval date. On December 15, 1997, FDA received SLR 001 for NDA 50-742. The supplemental labeling revision provided for a new 3 mg tablet formulation. The supplement was amended once during the course of the review with the submission received on June 24, 1998. The supplement was approved on October 8, 1998.

Review of Submissions:
The final printed labeling for NDA 50-742/S-001 dated, June 2, 1999, received June 8, 1999 was compared to the proposed draft labeling submitted December 12, 1997, received December 15, 1997, and approved on October 8, 1998.

Conclusions/Recommendations:
The final printed labeling dated June 2, 1999, received June 8, 1999 is identical to the proposed draft labeling submitted December 12, 1997, received December 15, 1997 and approved on October 8, 1998.. An Acknowledge and Retain letter should be drafted and forwarded to the sponsor.

Lisa M. Hubbard, R.Ph.
Senior Regulatory Management Officer,
HFD-590

Andrea Meyerhoff, M.D.
Medical Officer
HFD-590

cc:
NDAs 50-742
HFD-590/Division file
HFD-590/ActingDivDir/R. Albrecht
HFD-590/MedTL/R. Roca
HFD-590/MO/A. Meyerhoff
HFD-590/PM/V. Jensen

Concurrence:

HFD-590/ActingDivDir/R. Albrecht
HFD-590/MedTL/R. Roca

DFS keywords:
admin review
class, other
indic, other

/s/

Lisa Hubbard
9/15/00 12:24:35 PM
CSO

THIS IS A REVIEW REVISED AT RENATA'S SUGGESTION. pLEASE REVIEW AND SI
GN

Andrea Meyerhoff
1/24/01 09:43:24 AM
MEDICAL OFFICER

These copies are OFFICIAL FDA Copies
not desk copies.

Merck & Co., Inc.
West Point, PA 19486

ORIGINAL

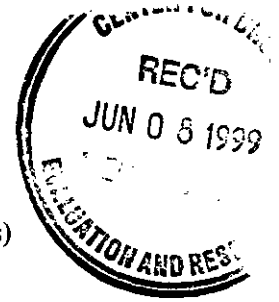
SCF-001/FA

June 2, 1999

MERCK
Research Laboratories

Mark Goldberger, MD, Director
Division of Special Pathogens and
Immunologic Drug Products, HFD-590, Rm. S-444
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA SUPPL AMEND



NDA 50-742/S-001: STROMECTOL™ (Ivermectin Tablets)
FINAL PRINTED LABELING

Dear Dr. Goldberger:

Reference is made to the Supplemental New Drug Application 50-742/S-001 for STROMECTOL™ submitted on December 12, 1997. Reference is also made to your approval letter dated October 8, 1998 regarding this supplemental application.

Attached for submission are the following:

1. A summary of revisions
2. An annotated circular, illustrating the revisions
3. Printed package circular #9032301 (20 copies)
4. Printed aluminum foil pouches (20 copies)
5. Printed carton (20 copies)

The circular has been revised to include the 3 mg tablet. The revised label will be used in all products sold or distributed on or before September 1, 1999.

Questions concerning this supplemental application should be directed to Frank Ricci (610/397-2975) or, in my absence, to Edwin Hemwall, Ph.D. (610/397-2306).

Sincerely,

Frank Ricci
Merck Research Laboratories
Division of Merck & Co., Inc.
Sumneytown Pike
West Point, PA 19486

q:graz/amy/SNDA3

Attachments
Certified No. P 971 230 003

NDA# 50-742

STROMECTOL®
(Ivermectin)

SUMMARY OF REVISIONS

The circular for STROMECTOL® has been revised as follows, to include the 3 mg tablet:

DESCRIPTION

Second paragraph: The availability of the 3 mg tablet is added.

DOSAGE AND ADMINISTRATION

Since the 3 mg tablet is an exact submultiple of the 6 mg tablet, the dosage is twice that of the 6 mg tablet. The dosage recommendations for the 3 mg tablet have been included under Tables 1 and 2.

HOW SUPPLIED

The availability of the 3 mg tablets in packages of 20 has been added.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-742/S-001

SEP 29 2000

Merck Research Laboratories
Attention: Frank Ricci
Sumney Pike, P.O. Box 4
BLA-33
West Point, PA 19486

Dear Mr. Ricci:

We acknowledge the receipt of your June 2, 1999 submission containing final printed labeling in response to our October 8, 1998 letter approving your supplemental new drug application (NDA) for Stromectol® (ivermectin) tablets, 3 mg and 6 mg.

We have reviewed the labeling that you submitted in accordance with our October 8, 1998 letter, and we find it acceptable.

If you have any questions, call Lisa M. Hubbard, R.Ph., Senior Regulatory Project Manager, at (301) 827-2127.

Sincerely,

S 9/29/00

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

050742_5001