DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-742/S-012, S-013

Attention: Tamra L. Goodrow, Ph.D.
Director, Regulatory Affairs
Merck & Co. Inc.
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Goodrow:

Please refer to your supplemental new drug applications, which were submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA #	Drug Product	Supplement Number	Letter Date	Receipt Date
50-742	Stromectal™ (ivermectin) Tablets, 3 mg and 6 mg	S-012	February 10, 2003	February 10, 2003
		S-013	August 13, 2003	August 14, 2003

We acknowledge the receipt of your submissions dated October 8, 2003 (S-013), and December 9, 2003 (S-012), and February 3, 2004 (S-012 and S-013).

Supplemental new drug application S-012 provides for the inclusion of new data from a Phase I food interaction study. There are changes in the **CLINICAL PHARMACOLOGY**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections.

Supplemental new drug application 013, submitted as a "Changes Being Effected" supplement, provides for the addition of "difficulty walking" to **PRECAUTIONS**, *General* and the addition of "toxic epidermal necrolysis" to **ADVERSE REACTIONS**, *Onchocerciasi*s.

The following revisions were made to the package insert (additions are <u>double underlined</u> and deletions are ~~strikethrough~~):

1. Throughout the package insert "µg" has been changed to "mcg".

2. **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 mcg/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 in man is approximately ~~at least 16~~ 18 hours following oral administration.

The ~~effect(s) of food on the systemic availability of ivermectin has not been studied~~safety and pharmacokinetic properties of ivermectin were further assessed in a multiple-dose clinical pharmacokinetic study involving healthy volunteers. Subjects received oral doses of 30 to 120 mg (333 to 2000 mcg/kg) ivermectin in a fasted state or 30 mg (333 to 600 mcg/kg) ivermectin following a standard high-fat (48.6 g of fat) meal. Administration of 30 mg ivermectin following a high-fat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30 mg ivermectin in the fasted state.

3. **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.

Rarely, patients with onchocerciasis who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: back pain, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, or coma. This syndrome has been seen very rarely following the use of ivermectin; a cause and effect relationship has not been established. In individuals who warrant treatment with ivermectin for any reason and have had significant exposure to *Loa loa*-endemic areas of West or Central Africa, pretreatment assessment for loiasis and careful post-treatment follow-up should be implemented.

Information for Patients

STROMECTOL should be taken ~~with water.~~on an empty stomach with water. (See CLINICAL PHARMACOLOGY, *Pharmacokinetics*.)

4. Under the **ADVERSE REACTIONS** section, the following changes were made:

Laboratory Test Findings

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

Onchocerciasis

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

5. 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~~ mcg of ivermectin per kg of body weight. See Table 1 for dosage guidelines. Patients should take tablets on an empty stomach with water. (See CLINICAL PHARMACOLOGY, *Pharmacokinetics*.) In general, additional doses are not necessary. However, follow-up stool examinations should be performed to verify eradication of ~~infection (see~~ infection. (See CLINICAL PHARMACOLOGY, *Clinical Studies*).

Onchocerciasis
The recommended dosage of STROMECTOL for the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 ~~µg~~ mcg of ivermectin per kg of body weight. See Table 2 for dosage guidelines. Patients should take tablets on an empty stomach with water. (See CLINICAL PHARMACOLOGY, *Pharmacokinetics*.) 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

We have completed the review of these supplemental applications, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted February 3, 2004).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved supplements NDA 50-742/S-012, S-013**." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Christine Lincoln, RN, MS, MBA, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

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