DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-742/S-017 and S-018

Merck & Co., Inc.
Attention: Ms. Mary Beth Wigley
Manager, Regulatory Affairs
770 Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Ms. Wigley:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for STROMECTOL™ (ivermectin) Tablets, 3 mg and 6 mg.

Supplement Number	Date of Supplement	Date of Receipt
S-017	July 20, 2005	July 21, 2005
S-018	September 1, 2005	September 2, 2005

We acknowledge receipt of your submission dated October 12, 2005 for NDA 50-742/S-018.

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the STROMECTOL™ package insert:

- Supplement 017 provides for the deletion of the text "a cause and effect relationship has not been established" in the **PRECAUTIONS:** *General* subsection.
- Supplement 018 provides for the addition of "seizure" in the **PRECAUTIONS:** *General* subsection and the addition of "seizures, elevation of liver enzymes, and elevation of bilirubin" in the **ADVERSE REACTIONS:** *Post-Marketing Experiences for All Indications* subsection.

Added text = <u>double underline</u> and Deleted text = ~~strikethrough~~

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, seizures, or coma. This syndrome has been seen very rarely following the use of ivermectin; ~~a cause and effect reason 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.

ADVERSE REACTIONS

Post-Marketing Experiences for All Indications

The following adverse reactions have been reported since the drug was registered overseas: hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, elevation of liver enzymes, and elevation of bilirubin.

We completed our review of these supplemental applications, as amended. These supplemental applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: ***Providing Regulatory Submissions in Electronic Format - NDAs*** (January 1999) and ***Providing Regulatory Submissions in Electronic Format – Content of Labeling*** (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review of the FPL and future submission, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "**FPL for approved supplements NDA 50-742/S-017 and S-018**." Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH: The FDA Safety Information and Adverse Event Reporting Program
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Mail Stop 4447
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Yon Yu, Pharm. D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
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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