DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-719/S-009

Prometheus Laboratories, Inc.
Attention: Henry Pan, M.D., Ph.D.
Executive VP, Chief Scientific and Chief Medical Officer
9410 Carroll Park Dr.
San Diego, CA 92121

Dear Dr. Pan:

Please refer to your supplemental new drug application dated February 6, 2007, received February 7, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HELIDAC® Therapy (bismuth subsalicylate/metronidazole/tetracycline hydrochloride).

We acknowledge receipt of your submission dated July 3, 2007.

This "Changes Being Effected" supplemental new drug application, submitted in response to the Agency's Supplement Request Letter dated December 11, 2006, provides for the following changes to the HELIDAC® Therapy package insert (deletions are indicated by ~~strikethrough~~ and additions are indicated by underline):

1. The **CLINICAL PHARMACOLOGY/Microbiology** subsection of the package insert was revised as follows:

   Susceptibility Testing of *Helicobacter pylori*: Susceptibility testing of ~~metronidazole against~~ *Helicobacter pylori* for metronidazole has not been standardized. No ~~susceptibility~~interpretive criteria have been established ~~Susceptibility criteria that have been established~~ for testing metronidazole against ~~anaerobic bacteria (not susceptible defined as MIC ≥ 16 µg/mL) are often used for testing~~ *H. pylori*. ~~However, these criteria may not be appropriate for~~ The clinical significance of metronidazole MIC values against *H. pylori* ~~testing and may not reflect clinical outcome~~ is unknown.

   ~~Metronidazole is a prodrug that must be reduced to an active form. Reduction requires a redox potential that is not achieved under *in vitro* microaerobic growth conditions favored by *H. pylori*. Anaerobic pre-incubation decreases metronidazole MICs obtained when testing *H. pylori*.~~

   ~~**Pretreatment Resistance:** Of the 49 patients enrolled in the P&GP study for whom pretreatment metronidazole susceptibility was determined by agar dilution, 22% (11/49) were classified as non-susceptible.~~

Metronidazole Susceptibility Test Results and Clinical/Bacteriologic Outcome: In the P&GP clinical study, 42.1% (24/57) of the patients in the intent-to-treat population who received HELIDAC Therapy did not have pretreatment metronidazole-susceptibility determined due to non-viability of the isolates or negative cultures.

The pre-treatment *Helicobacter pylori* metronidazole susceptibility results and the *H. pylori* eradication results post-treatment are shown in the table below.

Metronidazole Susceptibility Test Results and Clinical/Bacteriological Outcomes[a] for HELIDAC® Therapy (bismuth subsalicylate 525 mg, metronidazole 250 mg, and tetracycline hydrochloride 500 mg four times daily for 14 days)

Metronidazole Pre-treatment Results		***H. pylori* negative (Eradicated)**	***H. pylori* positive (Not Eradicated) Post-treatment Metronidazole Results**		
	N		MIC ≤ 8	MIC ≥ 16	No MIC
MIC ≤ 8 g/mL	26	23	1	2	0
MIC ≥ 16 g/mL	7	4	1	1	1

[a] Includes only patients with pretreatment metronidazole susceptibility test results

It is recommended that all patients not eradicated of *H. pylori* following bismuth subsalicylate, metronidazole, and tetracycline treatment be retreated with a regimen which does not contain metronidazole.

2. The following wording was removed from the **INDICATIONS AND USAGE** section of the label:

   It is recommended that all patients not eradicated of *H. pylori* following HELIDAC Therapy plus an H_2-antagonist, should be retreated with a regimen which does not contain metronidazole. (See **Microbiology** subsection.)

3. The following reference was updated:

   1. National Committee for Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Fifth Edition.; Approved Standard NCCLS DocumentSeventh Edition. Clinical and Laboratory Standards Institute Document M7-A5A7, Vol. 2026, No. 2, NCCLSCLSI, Wayne, PA, January 2006.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text dated July 3, 2007.

If you have any questions, please call Christine Lincoln, RN, M.S., MBA, Regulatory Health 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 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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