DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-719/S-007

Prometheus Labs
Attention: Marilyn Carlson, D.M.D., M.D.
Vice President of Medical/Regulatory Affairs, Chief Medical Officer
5739 Pacific Center Boulevard
San Diego, CA 92109

Dear Dr. Carlson:

Please refer to your supplemental new drug application dated January 27, 2003, received January 28, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Helidac® Therapy (bismuth subsalicylate/metronidazole/tetracycline hydrochloride).

This supplemental new drug application provides for the following changes to the for Helidac® Therapy package insert:

Added text = double underlined
~~Deleted text~~ = strikethrough

1. **CLINICAL PHARMACOLOGY**

   a. The **Microbiology** subsection has been revised to read:

      Microbiology: Bismuth subsalicylate, metronidazole, and tetracycline administered individually as combination therapy have been shown to be active against most strains of *Helicobacter pylori in vitro,* and in clinical infections as described in the **CLINICAL STUDIES** and **INDICATIONS AND USAGE** sections. ~~demonstrated *in vitro* activity against most susceptible strains of *Helicobacter pylori*.~~

   b. The **Helicobacter** subsection has been revised to read:

      Helicobacter: *Helicobacter pylori*: ~~Metronidazole resistance has been increasing in the U.S. and mostly occurs in patients previously treated with metronidazole. Some *H. pylori* strains isolated from patients treated with bismuth, metronidazole, and tetracycline demonstrate an increase in metronidazole MICs, indicating decreasing susceptibility.~~

      In the Graham and Cutler studies, ~~pretreatment and emerging resistance were not assessed~~ susceptibility testing was not performed for bismuth subsalicylate, metronidazole, or tetracycline~~, because susceptibility testing was not performed~~. No

adequate data were collected during the clinical studies to indicate that bismuth subsalicylate can either decrease or increase metronidazole ~~resistance~~ MICs. (See **CLINICAL STUDIES**.)

Susceptibility testing of *Helicobacter pylori* isolates was performed in the PG&P study for metronidazole using agar dilution methodology[1] and minimum inhibitory concentrations (MICs) were determined.

c. The subsection **Susceptibility Testing of *Helicobacter pylori*** has been moved to after the **Helicobacter** subsection and revised to read:

Susceptibility Testing of *Helicobacter pylori*: Susceptibility testing of metronidazole against *Helicobacter pylori* has not been standardized. No susceptibility 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 *H. pylori* testing and may not reflect clinical outcome.

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*.

d. The **Pretreatment Resistance** section was revised to read:

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 ~~resistant~~ non-susceptible.

e. The **Metronidazole Susceptibility Test Results and Clinical/Bacteriologic Outcome** section was revised to read:

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. ~~Of the patients receiving HELIDAC Therapy with pretreatment metronidazole susceptible MICs (≤ 8 µg/mL), 88.5% (23/26) were eradicated of *H. pylori* and 11.5% (3/26) failed therapy. Of the three patients who failed therapy, one had a post-treatment *H. pylori* isolate with a metronidazole susceptible MIC. The other two patients who failed therapy had post-treatment *H. pylori* isolates with metronidazole resistant MICs (≥ 32 µg/mL). Of the seven patients who had metronidazole-resistant isolates pretreatement, three were eradicated, one had a post-treatment isolate with a metronidazole susceptible MIC, one had a post-treatment isolate with a metronidazole resistant MIC, one had a negative culture, and one had no post-treatment susceptibility results.~~

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 Pretreatment Results		*H. pylori* negative (Eradicated)	*H. pylori* positive (Not Eradicated) Post-treatment Metronidazole Results		
	N		MIC ≤ 8	MIC ≥16	No MIC
MIC ≤ 8 µg/mL	26	23	1	2	0
MIC ≥16 µg/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. ~~considered to have *H. pylori* resistant to metronidazole.~~

f. The original **Susceptibility Tests for *Helicobacter pylori*** subsection has been removed.

~~**Susceptibility Tests for *Helicobacter pylori*:** The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[†] One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 to 1×10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (> 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for *Campylobacter* species. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism.~~

~~Results obtained from the P&GP study were determined using agar dilution methodology for metronidazole and bismuth subsalicylate. Tetracycline hydrochloride susceptibility was determined using the E-Test.~~

~~Breakpoints for bismuth subsalicylate, metronidazole, and tetracycline hydrochloride have not been standardized. For the purposes of this study, the following breakpoints were used:~~

~~**Classification**~~	~~**Metronidazole* (µg/mL)**~~	~~**Tetracycline HCl* (µg/mL)**~~	~~**Bismuth Subsalicylate[‡] (µg/mL)**~~
~~Resistant~~	~~≥ 32~~	~~≥ 16~~	~~≥ 256~~
~~Intermediate~~	~~16~~	~~8~~	~~128~~
~~Susceptible~~	~~≤ 8~~	~~≤ 4~~	~~≤ 64~~

~~* Based on NCCLS recommendations for anaerobes~~
~~† Based on empirical judgment~~

~~Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard metronidazole powders should provide the following MIC values:~~

~~**Microorganism**~~	~~**Antimicrobial Agent**~~	~~**MIC (µg/mL)**[a]~~
~~*H. pylori* ATCC 43504~~	~~Metronidazole~~	~~64 to 256 µg/mL~~

~~[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.~~

2. **INDICATIONS AND USAGE**

   a. The second paragraph was revised to read:

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

3. **REFERENCES**

   1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.
   ~~1. National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa, FL. January, 1997.~~

4. The manufacturers were updated as follows:

   Bismuth subsalicylate tablets are manufactured by ~~Procter and Gamble Pharmaceuticals~~ OSG Norwich Pharmaceuticals. Metronidazole 250-mg tablets, USP and tetracycline hydrochloride 500-mg capsules, USP are manufactured by ~~Zenith Goldline Pharmaceuticals, Inc~~ IVAX Pharmaceuticals, Inc.

We completed our review of this supplemental application, as amended. This application is 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).

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case 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 supplement NDA 50-719/S-006." Approval of this submission 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, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Kristen Miller, Pharm.D., Regulatory Project Manager, 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

Enclosure

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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