CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-793

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS

NDA #: #50-786

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 27-MAR-06
CDER DATE: 27-MAR-06
REVIEW ASSIGN DATE: 12-JUL-06
REVIEW COMPLETE DATE: 11-AUG-06

SPONSOR:
Axcan Scandipharm, Inc.
22 Inverness Parkway Suite 310
Birmingham, AL 35242

CONTACT PERSON:
Irma Monaco
Manager. Regulatory Affairs
Phone Number: (800) 615-4393

SUBMISSION REVIEWED: Amendment #23—Response to Action letter dated 10/2/2003

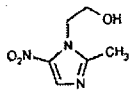
DRUG CATEGORY: Antibiotics plus proton pump inhibitor

INDICATIONS: *Helicobacter pylori* Eradication in Patients with Duodenal Ulcer Disease (active or by history)

DOSAGE FORM: Capsules—125 mg metronidazole, 140 mg biskalcitrate potassium, and a smaller capsule with 125 mg of tetracycline

DRUG PRODUCT NAME
PROPRIETARY: HELIZIDE ™/ PYLERA™ capsules
NONPROPRIETARY/USAN: biskalcitrate potassium, metronidazole, tetracycline

Metronidazole:
CHEMICAL NAME: 2-Methyl-5-nitroimidazole-ethanol
STRUCTURAL FORMULA:

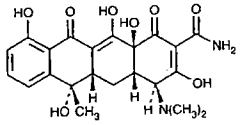


Molecular Formula: $C_6H_9N_3O_3$
Molecular Weight: 171.16

Tetracycline:

CHEMICAL NAME: (4*S*,4a*S*,5a*S*,12a*S*)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.

STRUCTURAL FORMULA:



Molecular Formula: $C_{22}H_{24}N_2O_8$
Molecular Weight: 444.44

SUPPORTING DOCUMENTS: [redacted] –Single-Triple Capsules for eradication of *H. pylori* in *H. pylori* infected patients.

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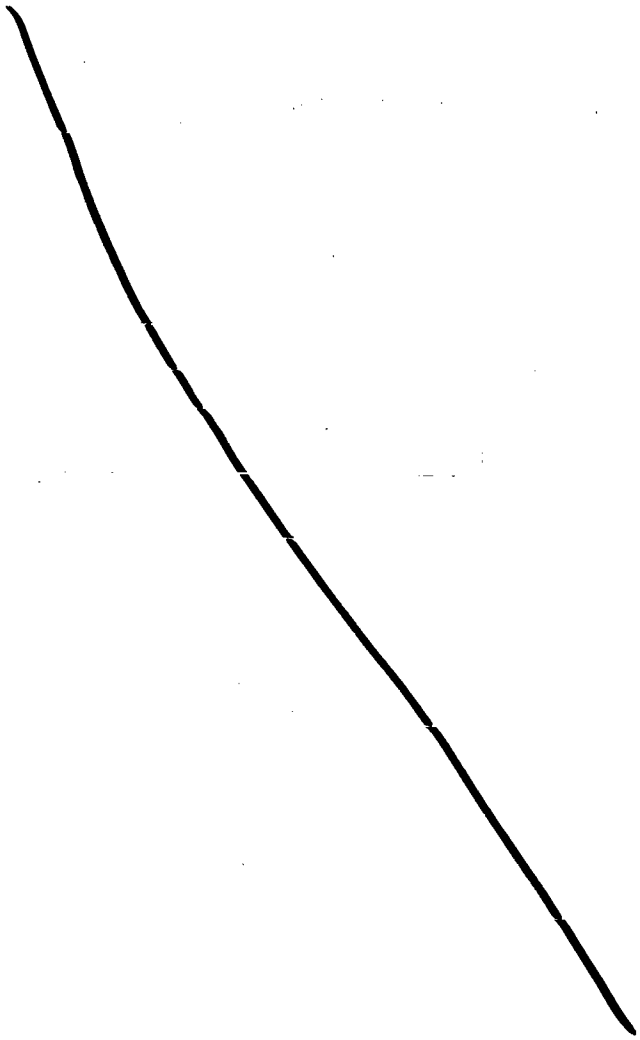
EXECUTIVE SUMMARY

The original NDA submitted in 2003 was NOT APPROVED due to the failure of the manufacturing site in [redacted] to pass manufacturing inspections. The applicant subsequently pursued a resubmission of the NDA, and in a face to face pre NDA (February 8, 2006) meeting with the company, the reviewers provided the following advice specific to labeling of PYLERA® for [redacted]



INTRODUCTION and BACKGROUND

The sponsor is seeking approval of Helizide capsules (biskalcitrate potassium, metronidazole, and tetracycline hydrochloride) in combination with omeprazole for the eradication of *Helicobacter pylori* in infected patients with duodenal ulcer disease (active or by history)

Each gelatin capsule contains 125 milligrams of metronidazole, 140 milligrams of biskalcitrate potassium, and a smaller capsule with 125 milligrams of tetracycline hydrochloride.

In this submission the sponsor responds to an action letter sent by FDA on February 3, 2006 requesting additional information on [redacted] In this letter FDA asked for the following information:

1. [redacted]
2.
3.
4.
5.

[redacted]

27 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Microbiology-1

Peter A. Dionne
Microbiologist DSPTP

CONCURRENCES:

DSPTP/Div Dir_____Signature_____Date
DSPTP/TLMicro_____Signature_____Date

CC:
DSPTP/Original NDA # 50-786
DSPTP/Division File
DSPTP/Micro/PDionne
DSPTP/MO/JMeyer
DSPTP/TMO/ENavarro
DSPTP/Pharm/SHundley
DSPTP/Chem/GHolbert
DSPTP/CSO/RSaville

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

/s/

Peter Dionne
9/26/2006 01:34:33 PM
MICROBIOLOGIST

Corrected Version

Shukal Bala
9/26/2006 01:37:44 PM
MICROBIOLOGIST

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: #50-786

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 28-SEP-01
CDER DATE: 02-OCT-01
REVIEW ASSIGN DATE: 02-NOV-01
REVIEW COMPLETE DATE: 18-JAN-02

SPONSOR:
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Manager U.S. Regulatory Affairs
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SUBMISSION REVIEWED: Original NDA for *H. pylori* eradication

DRUG CATEGORY: Antibiotics plus proton pump inhibitor

INDICATIONS: *Helicobacter pylori* Eradication in Patients with Duodenal Ulcer Disease (active or by history)

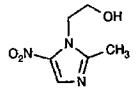
DOSAGE FORM: Capsules—125 mg metronidazole, 140 mg biskalcitrate potassium, and a smaller capsule with 125 mg of tetracycline

DRUG PRODUCT NAME

PROPRIETARY: HELICIDE ® capsules
NONPROPRIETARY/USAN: biskalcitrate potassium, metronidazole, tetracycline

Metronidazole:

CHEMICAL NAME: 2-Methyl-5-nitroimidazole-ethanol
STRUCTURAL FORMULA:

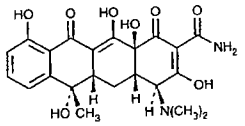


Molecular Formula: $C_6H_9N_3O_3$
Molecular Weight: 171.16

Tetracycline:

CHEMICAL NAME: (4*S*,4a*S*,5a*S*,12a*S*)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.

STRUCTURAL FORMULA:



Molecular Formula: $C_{22}H_{24}N_2O_8$
Molecular Weight: 444.44

SUPPORTING DOCUMENTS: [redacted] –Single-Triple Capsules for eradication of *H. pylori* in *H. pylori* infected patients.

REMARKS/COMMENTS:

This is an original New Drug Application for Helicide capsules (biskalcitrate potassium, metronidazole, and tetracycline hydrochloride), in combination with Omeprazole, for eradication of *Helicobacter pylori* in patients with duodenal ulcer disease.

CONCLUSIONS:

1. In the pivotal comparative study (HPST99-CUS01) 40.8% (51/125) of the *Helicobacter pylori* isolates in the clinical trial had metronidazole MICs ≥ 16 µg/mL. Treatment with Helicide plus omeprazole eradicated 82.4% (42/51) of these isolates. There were 74 isolates with metronidazole MICs ≤8 µg/mL. Treatment with Helicide plus omeprazole eradicated 90.5% (67/74) of these isolates. It appears that metronidazole MIC values do not correlate with clinical outcome. No breakpoint criteria have been established for metronidazole against *H. pylori*.

2. In the pivotal comparative study (HPST99-CUS01) 12.2% (14/115) of the *Helicobacter pylori* isolates in the clinical trial had clarithromycin MICs of ≥4 µg/mL (resistance is equal to MICs of ≥1 µg/mL). Treatment with clarithromycin plus amoxicillin plus omeprazole eradicated only 21.4 % (3/14) of these isolates. There were 101 isolates with clarithromycin MICs of ≤0.125 µg/mL. Treatment with clarithromycin plus amoxicillin plus omeprazole eradicated 92.1% (93/101) of these isolates. Clarithromycin MICs above 1.0 µg/mL have a much lower eradication rate than those below 1.0 µg/mL when treated with clarithromycin.

3. In the non-pivotal Phase II study (HPST98-INT01) 29.5% (38/129) of the *Helicobacter pylori* isolates in the clinical trial had metronidazole MICs ≥ 16 µg/mL. Treatment with Helicide plus omeprazole eradicated 92.1% (35/38) of these isolates. There were 91 isolates with metronidazole MICs ≤ 8 µg/mL. Treatment with Helicide plus omeprazole eradicated 95.6% (87/91) of these isolates. Once again there is no correlation between metronidazole MICs and clinical outcome.

4. In study HPST99-CUS01 changes in susceptibility to clarithromycin and metronidazole were assessed in organisms isolated from patients whose study treatment failed to eradicate *H. pylori.* There were only a few failures and most patients refused to have a second endoscopy after treatment. In the seven patients who had metronidazole MICs of ≤ 8 µg/mL who failed only two had a repeat culture. One isolate had a metronidazole MIC of 2 µg/mL pre-therapy and 128 µg/mL post-therapy. The other isolate had a MIC of 8 µg/mL pre-therapy and 128 µg/mL post-therapy. In the 9 failures that had metronidazole MICs ≥16 µg/mL, four had repeat cultures. One patient with a metronidazole MIC of 32 µg/mL at baseline had a post-therapy metronidazole MIC of 128 µg/mL, two other patients with baseline MICs of 128 µg/mL had post-therapy MICs of 256 µg/mL, and one patient with a baseline MIC of 256 µg/mL had a post-therapy MIC of 128 µg/mL. Although there is very little data, it appears that treatment with metronidazole does not increase MIC values.

RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act. Minor changes should be made to the microbiology subsection of the label. The revised Microbiology section of the labeling is attached on pages 24-27 of this review.

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IN VITRO ACTIVITY AGAINST *H. PYLORI*

Omeprazole

Four studies were submitted that tested the susceptibility of *Helicobacter pylori* to omeprazole. Three studies used the agar dilution method. The inoculum varied from 10^4 to 10^6 CFU/spot. The other study (7) used a broth microdilution method. TABLE 1 summarizes these studies.

TABLE 1
Susceptibility of *Helicobacter pylori* to Omeprazole

Reference:	Number of Isolates Tested	MIC_{50} (µg/mL)	Range (µg/mL)	MIC_{90} (µg/mL)
6	42	---	32-64	---
7	6	---	4-8	---
8	89	≤8	≤8	≤8
9	53	16	4-64	16

These data demonstrate that omeprazole has a limited amount of activity against *Helicobacter pylori.*

Biskalcitrate potassium (colloidal bismuth)

Four studies were submitted that tested the susceptibility of *Helicobacter pylori* to bismuth salts. All studies used the agar dilution method. The inoculum varied from 5 x 10^4 to 10^6 CFU/spot. TABLE 2 summarizes these studies.

TABLE 2
Susceptibility of *Helicobacter pylori* to Bismuth Salts

Reference:	Number of Isolates Tested	MIC_{50} (µg/mL)	Range (µg/mL)	MIC_{90} (µg/mL)
6	42	64	16-128	64
10	13	---	6.5-12	---
11	70	8	2-32	16
9	53	16	4-32	16

The data in the above table show that bismuth salts have some limited *in vitro* activity on *Helicobacter pylori* when tested by themselves.

EXECUTIVE SUMMARY

The sponsor is seeking approval of Helicide capsules (biskalcitrate potassium, metronidazole, and tetracycline hydrochloride) in combination with omeprazole for the eradication of *Helicobacter pylori* in infected patients with duodenal ulcer disease (active or by history)

Each gelatin capsule contains 125 milligrams of metronidazole, 140 milligrams of biskalcitrate potassium, and a smaller capsule with 125 milligrams of tetracycline hydrochloride.

The application consists of two studies. Treatment was for 10 days in both studies.

Protocol HPST99-CUS01—This was a pivotal study that compared Helicide four times a day given with omeprazole (20 mg twice a day) to omeprazole (20 mg) plus amoxicillin (1 gram) and clarithromycin (500 mg) given twice a day. The effect of *Helicobacter pylori* resistance to metronidazole and clarithromycin on the efficacy of these treatments was assessed. This study was conducted in the United States and Canada.

Protocol HPST99-INT01—This was a supportive study with no comparator. It was an open label, multicenter international Phase III study conducted in Australia, Europe, and North America. The effect of metronidazole resistance on efficacy was assessed.

In both studies a metronidazole MIC of ≥8 µg/mL was considered to be resistant. No breakpoints for metronidazole against *Helicobacter pylori* have been established. Since the [redacted] anaerobic breakpoints for metronidazole were used, the isolates with a MIC of 8 µg/mL should be considered susceptible and not resistant. The correct methodology that should be used to assess susceptibility has also not been established. The breakpoints that are usually used were determined for anaerobic organisms. *Helicobacter pylori* is not an obligate anaerobe and metronidazole which inhibits anaerobic growth after reduction under anaerobic conditions may not have the same mechanism of action or activity against *H. pylori.* In the CUS01 study 67/74 (90.5%) of the metronidazole susceptible isolates (MICs ≤8 µg/mL) were eradicated and 42/51 (82.4%) of the metronidazole resistant isolates (MICs ≥15 µg/mL) were eradicated by the Helicide plus omeprazole treatment. This was not a significant difference. On the other hand, 93/101(92.1%) of the clarithromycin susceptible isolates were eradicated but only 3/14 (21.4%) of the clarithromycin resistant isolates were eradicated by treatment with clarithromycin plus amoxicillin plus omeprazole. In study INT01, 87/91 (95.6%) of the metronidazole susceptible isolates were eradicated and 35/38 (92.1%) of the metronidazole resistant isolates were eradicated by Helicide plus omeprazole treatment.

PRECLINCIAL EFFICACY (*IN VITRO)*

MECHANISM OF ACTION

Omeprazole

Omeprazole is a proton pump inhibitor. It is a specific antagonist of the gastric parietal cell proton pump. Through inhibition of the H^+/K^+ -ATPase in these cells, the drug decreases acid output.

It is not clear how omeprazole enhances the effect of antibiotics, but two theories have been proposed. *Helicobacter pylori* has evolved to live in an acid environment and seems to have a requirement for a small amount of acid. Omeprazole decreases acid output and may render the organism more vulnerable to the effect of an antibiotic. Alternatively there are certain antibiotics which are increasingly active as the pH increases. Omeprazole suppresses acid production and may, therefore, enhance the activity of these antibiotics.

Omeprazole has also been shown to be a potent inhibitor of urease (1). At a concentration of ≥25 µg/mL, it abolished urease activity and inhibited *H. pylori* toxin-induced cell vacuolation by 75%. A concentration of 5 µg/mL inhibited urease activity by 50%. *H. pylori* urease is important in the organism's ability to colonize the gastric mucosa.

Omeprazole can reduce the population of *H. pylori* colonizing the gastric antrum to the extent that the organisms may not be detected on gastric biopsy during omeprazole therapy (2). This clearance is transient, however, and *H. pylori* colonization returns to pretreatment levels after omeprazole has been discontinued.

Biskalcitrate potassium (colloidal bismuth)

The mechanism of action of biskalcitrate potassium and other bismuth salts is not well understood. One theory suggests that biskalcitrate inhibits the bacteria from adhering to the gastric mucus (3,4). Once detached, the inactivated bacteria drift through the mucus layer, approach the hostile environment of the gastric lumen and are swept away. Bismuth compounds may also inactivate bacterial enzymes and disrupt cell metabolism. This leaves the bacteria more susceptible to the body's normal defenses (4). Electron microscopy was used on biopsy specimens from infected patients, within two hours of oral administration of colloidal bismuth subcitrate. Bismuth was seen deposited in aggregates on the surface and within the bacteria. The location of the bacteria was changed from beneath the gastric mucus layer to within it, suggesting a loss of adherence to the epithelium.

Metronidazole

Metronidazole is active against a wide variety of anaerobic bacteria and protozoan parasites. It is metabolically activated through reductive pathways involving a number of different endogenous reduced substrates. The reduction of the nitro group on metronidazole generates labile, reactive intermediates that are thought to mediate the action of the drug.

Neither the mode of action nor the mechanism of resistance to metronidazole is completely understood in *Helicobacter pylori* (5). The cytotoxicity of metronidazole is not directly due to the final products of reduction but to the unstable and/or less reduced intermediates which damage DNA, resulting in strand breakage, helix destabilization, unwinding, and cell death. Reduction activation of metronidazole depends on the redox system of the target cells. Any redox systems in the cell possessing a reduction potential more negative than that of metronidazole will donate its electrons preferentially to metronidazole. The direct donors of electrons in anaerobic bacteria are thought to be ferredoxin-like Fe-S electron transport proteins such as ferredoxin. In anaerobic organisms, the redox potential is between –430 and –460 mV (millivolts), the typical value of ferredoxin-like Fe-S proteins. Metronidazole has a reduction potential of –415 mV, making metronidazole an efficient electron acceptor. The lowest redox potentials obtainable by aerobic organisms are those of the NAD/NADH (-320 mV) and NADP/NADPH (-324 mV) pathways. Aerobic organisms are, therefore, resistant to metronidazole. Six electrons would theoretically be involved in the complete reduction of a nitro ($-NO_2$) group of metronidazole to an amine or amino group ($-NH_2$). The reduction of a nitro group by one electron step yields a nitro free radical, and a hydroxylamine derivative. Under aerobic conditions, however, one electron step can be reoxidized by oxygen to the original compound, producing inactive metronidazole. Metronidazole resistance in *Helicobacter pylori* seems to be the result of inhibition of metronidazole nitroreductase activities. Mutations in these genes result in the production of truncated or inactivated enzymes that are incapable of reducing metronidazole to the active form.

Tetracycline

Tetracycline interacts with the 30S subunit of the bacterial ribosome and inhibits protein synthesis. The site of action of the tetracyclines is the bacterial ribosome. An energy dependent system (active transport) is needed for the drug to get into bacterial cells. These drugs inhibit protein synthesis by binding to 30S ribosomes. They prevent access of aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex. This prevents the addition of amino acids to the growing peptide chain. Only a small portion of the drug is irreversibly bound, and washing can reverse the inhibitory effects of the tetracyclines.

Metronidazole

Several studies have been submitted that tested the susceptibility of *Helicobacter pylori* to metronidazole. Some studies used the E-test strip to test susceptibility and a few studies compared the E-test method with the agar dilution method. Two studies used the broth microdilution method. TABLE 3 summarizes these studies.

TABLE 3
Susceptibility of *Helicobacter pylori* to Metronidazole

Reference	Number of Isolates Tested	Method Used	MIC_{50} (µg/mL)	Range (µg/mL)	MIC_{90} (µg/mL)
6	42	E-Test	---	0.06-1 (20 isolates) 64-256 (22) 8 (1)	---
7	23	Broth Microdilution	---	1-4	-----
8	89	Agar dilution	2	0.5->16	>16
11	70	Agar dilution	1	0.5-8	8.0
12	88	E-test	---	0.06-8 (64%) ≥256 (36%)	---
13	10	Microdilution	---	1.25-40	---
9	559	Agar dilution	---	0.5->128	---
14	53	Agar dilution	2	0.5-128	16
		Anaerobic Pre-Incubation	0.25	0.03-1	0.5
15	55	Agar dilution	2	0.25->64	16

The data in the above table demonstrate that there is a wide range of MIC values for metronidazole against *H. pylori*.

The E-test method gives results that are not comparable to the standard agar dilution method. Osato (16) compared the E-test method with agar dilution for over 3000 isolates. The E-test gave results that differed from the agar dilution method by more than 2 logs for 42% of the tested isolates. A change in susceptibility category (from susceptible to resistant) was seen for 17.6% of the isolates tested. Weiss (15) compared the E-test method and agar dilution methods against 55 isolates. The E-test gave results that differed from the agar dilution test by more than 2 logs for 36% of the isolates. It appears that the E-test method over estimates metronidazole resistance of *H. pylori* when compared to other test methods.

Rubinstein (9) demonstrated that anaerobic pre-incubation lowers metronidazole MICs considerably especially for the so called "resistant" strains. The authors suggest that enzymes are induced under microaerophilic but not under anaerobic conditions. These enzymes prevent the formation of ions that damage the bacterial DNA.

(17) suggests that metronidazole presents an unique if not insurmountable dilemma for laboratory test personnel. Metronidazole is a prodrug belonging to the nitroimidazole class of compounds. To be active, the prodrug must be reduced. Reduction requires a redox potential of at least –415 mV. These conditions are not achieved under microaerobic growth conditions favored by *H. pylori*. Under conditions that allow reduction of the prodrug (anaerobic conditions) *H. pylori* grows poorly if at all. Because susceptibility testing is based upon moderate to rapid growth of the test organism *in vitro*, such slow replication of *H. pylori* under the anaerobic conditions required to achieve activation of metronidazole further complicates susceptibility testing of this drug.

Tetracycline

Four studies were submitted that tested the susceptibility of *Helicobacter pylori* to tetracycline. TABLE 4 summarizes these studies.

TABLE 4
Susceptibility of *Helicobacter pylori* to Tetracycline

Reference	Number of Isolates Tested	Method Used	MIC_{50} (µg/mL)	Range (µg/mL)	MIC_{90} (µg/mL)
12	88	E-Test	---	≤4	---
13	10	Broth Microdilution	---	0.015-0.6	-----
9	53	Agar dilution	0.12	0.06-1	0.25
15	55	Agar dilution	0.125	≤0.03-0.5	0.25

The data in the above table demonstrate that tetracycline has good activity against most strains of *Helicobacter pylori*.

MECHANISM(S) OF RESISTANCE

Biskalcitrate potassium (colloidal bismuth)

Since very little is known on how bismuth salts inhibit *Helicobacter pylori* there is very limited if any data on resistance to these compounds. No studies on resistance were included in this submission. Since bismuth is being used primarily to aid tetracycline and metronidazole antibacterial activity, resistance to the action of bismuth is not a primary concern.

Metronidazole

Mechanisms of resistance to metronidazole have been most extensively studied in laboratory strains and clinical isolates of *Trichomonas.* It is unknown if these mechanisms of resistance are applicable to resistance in *Helicobacter pylori.* Both aerobic and anaerobic mechanisms of resistance have been demonstrated. Anaerobic resistance to metronidazole, which has been shown only in laboratory studies of *Trichomonas vaginalis* and *Trichomonas foetus* strains exposed to increasing concentrations of the drug in culture, appears to result from decreased or absent activity of enzymes within the hydrogenosome, an unique organelle that is the site of glycolysis in these organisms. Strains of *Trichomonas vaginalis* isolated from human patients with refractory cases of trichomoniasis display an aerobic type of resistance to metronidazole that can be detected only when the organisms are grown in the presence of oxygen. These metronidazole-resistant strains have been shown to contain decreased levels of ferredoxin, the protein that catalyses reaction of metronidazole in these organisms. It is probably this aerobic resistance that is important in *Helicobacter pylori* since it does not grow well if at all under anaerobic conditions.

As mentioned above susceptibility testing of *Helicobacter pylori* for metronidazole is complicated by the fact that anaerobic conditions are needed for the drug to be reduced to an active form and *H. pylori* needs oxygen to grow rapidly enough to do susceptibility testing. Rubinstein (9) has shown that strains isolated from patients with MICs of 16-128 μg/mL had MICs of 0.12-1 μg/mL when the organisms were subjected to an initial 16 hour anaerobic pre-incubation before antibiotic sensitivity testing was performed.

Tetracycline

Microorganisms that have become resistant to one member of the class frequently exhibit resistance to the other members of the tetracycline class. Resistance to the tetracyclines is primarily plasmid-mediated and is an inducible trait. There are three main resistance mechanisms.

1. Decreased accumulation of tetracycline as a result of either decreased antibiotic influx or acquisition of an energy-dependent efflux pathway.
2. Decreased access of tetracycline to the ribosome because of the presence of ribosome protection proteins, and
3. Enzymatic inactivation of tetracyclines.

Although there are examples of *Helicobacter pylori* strains that are resistant to tetracycline, the incidence appears to be rare (5, 14). The current rate of tetracycline resistance in *H. pylori* in the United States is sufficiently low and susceptibility testing for this drug is usually not performed (15).

PRECLINCIAL EFFICACY *(IN VIVO)*

PHARMACOKINETICS/BIOAVAILABILITY

The dosage regimen in this application uses Helicide capsules containing 140 mg of biskalcitrate potassium, 125 mg of metronidazole, and a smaller capsule containing 125 mg of tetracycline. Three of these capsules are to be taken four times a day in conjunction with omeprazole 20 mg twice a day for 10 days.

The information in this section is taken from the NDA studies submitted by the applicant and had not been reviewed by a Biopharmaceutical Reviewer at the time this review was written.

Following oral administration of biskalcitrate potassium, the plasma concentration reaches steady state after about 4 to 5 weeks of chronic administration. Absorbed bismuth continues to be excreted for about 12 weeks after stopping therapy. The elimination half-life is about 5 days.

Following oral administration, metronidazole is well absorbed, with peak plasma levels occurring between one and two hours after dosing. Plasma concentrations are proportional to the administered dose, with a 500 mg dose producing a peak plasma concentration of 13 µg/mL. The average elimination half-life is 8 hours.

Tetracyclines are well absorbed after oral dosing (60-90%). They are concentrated in the bile and excreted in the urine and feces.

When the pharmacokinetic profile of the Helicide capsule was compared to the profile from the components of the capsule given separately, the time to peak concentration (T_{max}) and the elimination half-lives ($T_{1/2}$) were similar whether the components were taken as Helicide or as separate capsules. The C_{max} and AUC parameters for metronidazole after Helicide capsule administration were bioequivalent to those after metronidazole was taken as a separate capsule. For tetracycline or bismuth the C_{max} and AUC values were less when Helicide capsules were taken versus when separate capsules were taken. Food significantly reduced the rate and extent of absorption of all three Helicide components. The AUC values for metronidazole, tetracycline, and bismuth were reduced by 6%, 34%, and 60%, respectively, when given with food. This food effect may be helpful in the eradication of *H. pylori*. It may keep the drugs in the intestinal tract for a longer time period. Helicide pharmacokinetic parameters are summarized in TABLE 5.

TABLE 5
Pharmacokinetic Parameters of Helicide in Fasted and Fed States

	FED			FASTED		
	Metronidazole	Tetracycline	Bismuth	Metronidazole	Tetracycline	Bismuth
C_{max} (µg/mL)	6.76	4.84	14.14	8.45	6.63	7.25
AUC_T (µg.h/mL)	76.95	5.26	8.25	82.02	7.99	20.09
AUC (µg.h/mL)	78.21	5.54	12.49	83.41	8.34	28.03

C_{max} = maximum serum concentration
AUC = Area Under the Concentration Time Curve

ANIMAL MODELS

Most animal models are not adequate for the study of *Helicobacter pylori* gastrointestinal infection. *H. pylori* infections have been established in piglets (18) and rats (19); however, these species do not develop ulcers. Ferrets are known to develop gastritis and ulcers as a natural disease. The disease appears to be associated with *Helicobacter mustelae* infection (20). The obvious limitation of the ferret model is that *H. pylori* is not the organism involved, thus the relevance to human disease is unclear.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

Both a pivotal study and a supportive study were performed by the sponsor and submitted in the application. These studies are summarized below.

PROTOCOL HPST99-CUS01

Efficacy and Safety of Quadruple Therapy by Single-Triple Capsules of Bismuth Subcitrate, Metronidazole, and Tetracycline HCl Given with Omeprazole in Eradication of *Helicobacter pylori*: A Comparison to Omeprazole + Amoxicillin + Clarithromycin.

This is a randomized, parallel-group, evaluator-blinded, active controlled study. Subjects in one arm of the study were given three Helicide capsules four times a day and 20 mg of omeprazole twice a day for 10 days. Subjects in the second arm of the study were given omeprazole 20 mg, amoxicillin 1 gram, and clarithromycin 500 mg twice a day for 10 days.

To be included in the trial, subjects must have been *Helicobacter pylori* positive as documented by a C-13 urea breath test (UBT) plus histology or culture and have a current duodenal ulcer or a history of duodenal ulcer in the previous five years.

The presence of *H. pylori* was first determined with a C-13 urea breath test, performed by a central laboratory [redacted]) using a FDA-approved test. Following confirmation of *H. pylori*, six biopsy samples were collected by endoscopy. One biopsy sample was used to detect *H. pylori* using the rapid urease test. Two samples were used for histological analysis, and two were used for culture. For histology, samples were immediately fixed in 10% buffered formalin, and *H. pylori* was presumptively identified by its morphology, with slides read and graded by the number of bacteria per high power magnification field. Samples were cultured on agar plates and *H. pylori* presumptively identified by morphology. The colonies were small, translucent and glistening with a convex elevation. Definitive identification was based on positive reactions to oxidase, catalase, and urease biochemical tests.

Testing for metronidazole, clarithromycin, tetracycline, and amoxicillin susceptibility was done at a central laboratory [redacted] . The agar dilution method was used and the National Committee for Clinical Laboratory Standards (NCCLS) methods for measuring the susceptibility of *Helicobacter pylori* were used. *H. pylori* ATCC 43504 was used as a Quality Control strain.

Eradication of *H. pylori* was determined using the C-13 urea breath test. One test was carried out at least 4 weeks after the end of treatment, and a second test was carried out at a confirmation visit at a minimum of 8 weeks after the end of treatment.

TABLE 6 summarizes the microbiological results of treatment for patients who received the Helicide treatment in the modified intent-to treat (MITT) population. Results are given by metronidazole MIC value.

TABLE 6
Results of Treatment with Helicide (Study CUS-01)

Metronidazole MIC (µg/mL)	Number of Isolates	Eradicated (%)	Failures (%)
0.25	4	4 (100%)	0
0.5	18	17 (94.4%)	1 (5.6%)
1	33	30 (90.9%)	3 (9.1%)
2	11	9 (81.8%)	2 (18.2%)
4	7	7 (100%)	0
8	1	0	1 (100%)
15	1	1 (100%)	0
16	4	4 (100%)	0
32	12	11 (91.7%)	1 (8.3%)
64	16	13 (81.3%0	3 (18.7%)
128	14	10 (71.4%)	4 (28.6%)
256	4	3 (75.0%)	1 (25.0%)
Total	125	109 (87.2%)	16 (12.8%)

NCCLS Metronidazole Breakpoints (Anaerobes)

Classification	Metronidazole MIC (µg/mL)
Susceptible	≤8
Intermediate	16
Resistant	≥32

In this study, however, they have classified MICs of 8 µg/mL and above as resistant. If MIC ≤8 µg/mL are considered susceptible then there were 7 failures out of 74 (9.5%) and 67/74 successes (90.5%). For the isolates with MICs >8 (should be stated as ≥16 µg/mL—the isolate with a MIC of 15 µg/mL is probably an error and should be 16 µg/mL) there were 9/51 failures (17.6%) and 42/51 (82.4%) successes.

TABLE 7 summarizes the microbiological results of treatment for patients who received the amoxicillin plus clarithromycin treatment in the modified intent-to treat (MITT) population. Results are given by clarithromycin MIC value.

TABLE 7
Results of Treatment with Amoxicillin + Clarithromycin (Study CUS-01)

Clarithromycin MIC (µg/mL)	Number of Isolates	Eradicated (%)	Failures (%)
0.015	20	17 (85%)	3 (15%)
0.03	48	46 (95.8%)	2 (4.2%)
0.06	31	28 (90.3%)	3 (9.7%)
0.125	2	2 (100%)	0
4	2	0	2 (100%)
8	3	1 (33.3%)	2 (66.7%)
16	9	2 (22.2%)	7 (77.8%)
Total	115	96 (83.5%)	19 (16.2%)

NCCLS approved breakpoints for clarithromycin against *Helicobacter pylori* are given below:

NCCLS Clarithromycin Breakpoints for *H. pylori*

Classification	Clarithromycin MIC (µg/mL)
Susceptible	≤0.25
Intermediate	0.5
Resistant	≥1.0

Using the NCCLS approved breakpoints there were 8/101 (7.9%) failures among the susceptible isolates and 93/101 (92.1%) successes. Among the resistant isolates there were 11/14 (78.6%) failures and only 3/14 (21.4%) successes.

Microbiological outcome is clearly correlated with clarithromycin-resistance but is not correlated with metronidazole-resistance. This is why clarithromycin breakpoints for *Helicobacter pylori* have been established and no breakpoints for metronidazole against *H. pylori* have been established.

Changes in susceptibility to clarithromycin and metronidazole were assessed in organisms isolated from patients whose study treatment failed to eradicate *H. pylori*. Many patients, unfortunately, refused to have a second endoscopy after treatment. Available results are presented for the MITT population in TABLE 8. An insufficient number of isolates are available to draw any meaningful conclusion.

TABLE 8
Change in Drug Susceptibility During Treatment (MITT Population)

Susceptibility to Metronidazole at baseline	*H. pylori* not eradicated	Susceptibility at second endoscopy			Susceptibility to Clarithromycin at baseline	*H. pylori* not eradicated	Susceptibility at second endoscopy		
		R	S	M			R	S	M
Resistant	9	4		5	Resistant	11	8		3
Susceptible	7	2		5	Susceptible	8	1	1	6
Missing	1			1	Missing	4	1		3
Total	17				Total	23			

R = resistant; S = susceptible; M = Missing

In the patients treated with metronidazole baseline isolates with metronidazole MICs of 2 µg/mL and 8 µg/mL (considered susceptible) had post-therapy metronidazole MICs of 128 µg/mL (considered resistant). One patient with a metronidazole MIC of 32 µg/mL at baseline had a post-therapy metronidazole MIC of 128 µg/mL, two other patients with baseline MICs of 128 µg/mL had post-therapy MICs of 256 µg/mL, and one patient with a baseline MIC of 256 µg/mL had a post-therapy MIC of 128 µg/mL.

In the patients treated with clarithromycin one patient with an isolate with a baseline clarithromycin MIC of 0.015 µg/mL had a post-therapy MIC of 0.015 µg/mL (both susceptible). Another patient with a baseline isolate with a MIC of 0.03 µg/mL (susceptible) had a post-therapy isolate with a MIC of 8 µg/mL (resistant). Two patients with baseline isolates with MICs of 4 µg/mL had post-therapy isolates with MICs of 16 µg/mL, one patient had both baseline and post-therapy isolates with MICs of 8 µg/mL, one patient with a baseline isolate with a MIC of 16 µg/mL had a post-therapy isolate with a MIC of 8 µg/mL, and four patients with baseline isolates with MICs of 16 µg/mL had post-therapy isolates with MICs of 16 µg/mL.

PROTOCOL HPST99-INT01

Efficacy and Safety of Quadruple Therapy by Single-Triple Capsules of Bismuth Subcitrate, Metronidazole, and Tetracycline HCl Given with Omeprazole in Eradication of *Helicobacter pylori*.

This was a multicenter, open-label, uncontrolled trial. Subjects were given three Helicide capsules four times a day and 20 mg of omeprazole twice a day for 10 days.

To be included in the trial, subjects must have been *Helicobacter pylori* positive as documented by a C-13 urea breath test (UBT) plus histology or culture.

The presence of *H. pylori* was first determined with a C-13 urea breath test, performed by a central laboratory [redacted]. Following confirmation of *H. pylori*, five biopsy samples were collected by endoscopy. One biopsy sample was used to detect *H. pylori* using the rapid urease test. The other four samples were used for histology and to assess metronidazole and clarithromycin resistance. For histology, *H. pylori* was presumptively identified by its morphology. Slides were read at the local laboratory and graded according to the amount of growth.

Metronidazole sensitivity testing was done at a central laboratory [redacted] by agar dilution.

Eradication of *H. pylori* was determined using the C-13 urea breath test. Two negative urea breath tests at approximately four weeks and eight weeks after the end of therapy confirmed eradication.

TABLE 9 summarizes the microbiological outcome for patients in the modified intent-to treat (MITT) population. Results are given by metronidazole MIC value.

TABLE 9
Results of Treatment with Helicide (Study INT-01)

Metronidazole MIC (µg/mL)	Number of Isolates	Eradicated (%)	Failures (%)
0.023	1	1 (100%)	0
0.25	5	5 (100%)	0
0.5	13	13 (100%)	0
1	15	14 (93.3%)	1 (6.7%)
2	38	35 (92.1%)	3 (7.9%)
4	13	13 (100%)	0
5	1	1 (100%)	0
8	5	5 (100%)	0
16	5	5 (100%)	0
32	9	9 (100%)	0
54	1	1 (100%)	0
64	17	14 (82.4%)	3 (17.6%)
128	6	6 (100%)	0
Total	129	109 (87.2%)	16 (12.8%)

There were 91 patients with isolates that had metronidazole MICs of ≤ 8 µg/mL. In these patients 4/91 (4.4%) isolates persisted and 87/91 (95.6%) were eradicated. There were 38 patients with isolates that had metronidazole MICs of ≥16 µg/mL. In these patients 3/38 (7.9%) isolates persisted and 35/38 (92.1%) were eradicated. Once again there appears to be no correlation between metronidazole MICs and microbiological outcome.

9 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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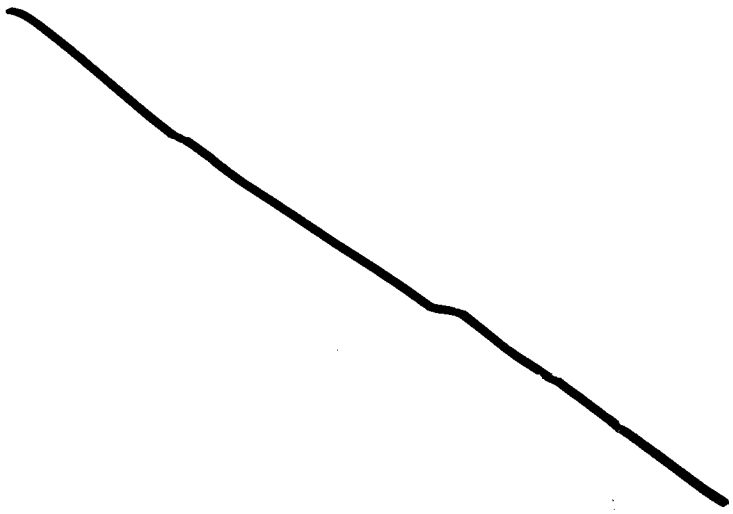

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