

DRAFT

DRAFT

HELIDAC® Therapy

(bismuth subsalicylate/metronidazole/tetracycline hydrochloride)

DRAFT

THESE PRODUCTS ARE INTENDED ONLY FOR USE AS DESCRIBED. The individual products contained in this package should not be used alone or in combination for other purposes. The information described in this labeling concerns only the use of these products as indicated in this combination package. For information on use of the individual components when dispensed as individual medications outside this combined use for treating *Helicobacter pylori*, please see the package inserts for each individual product.

WARNING

Metronidazole has been shown to be carcinogenic in mice and rats. (See **PRECAUTIONS**.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the **INDICATIONS AND USAGE** section below.

DRAFT

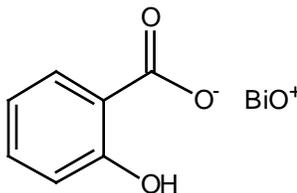
DESCRIPTION: HELIDAC Therapy consists of 112 bismuth subsalicylate 262.4-mg chewable tablets, 56 metronidazole 250-mg tablets, USP, and 56 tetracycline hydrochloride 500-mg capsules, USP, for oral administration.

DRAFT

Bismuth subsalicylate chewable tablets: Each pink round tablet contains 262.4 mg bismuth subsalicylate (102 mg salicylate) for oral administration.

Bismuth subsalicylate is a fine, white, odorless, and tasteless powder that is stable and non-hygroscopic. It is a highly insoluble salt of trivalent bismuth and salicylic acid.

Bismuth subsalicylate is 2-Hydroxybenzoic acid bismuth (3+) salt with the following structural formula:



Molecular weight: 362.11

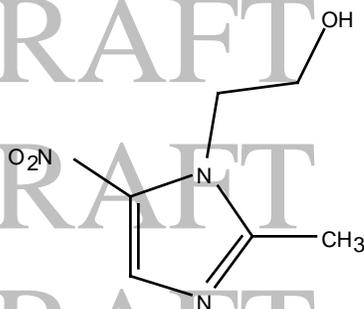
DRAFT

Inactive Ingredients: Each bismuth subsalicylate chewable tablet contains calcium carbonate, D&C Red No. 27 aluminum lake, flavor, magnesium stearate, mannitol, povidone, saccharin sodium, and talc.

DRAFT

DRAFT

Metronidazole tablets, USP: Each white round tablet contains 250 mg metronidazole. Metronidazole is 2-Methyl-5-nitroimidazole-1-ethanol, with the following structural formula:

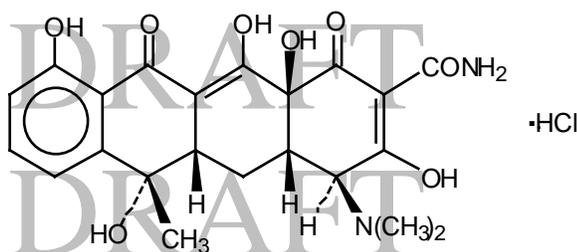


Molecular weight: 171.16

Inactive Ingredients: Each metronidazole tablet contains lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, and stearic acid.

Tetracycline hydrochloride capsules, USP: Each pink and white capsule contains 500 mg tetracycline hydrochloride, causing it to appear pale orange and white in color when filled. Tetracycline is a yellow, odorless, crystalline powder. Tetracycline is stable in air but exposure to strong sunlight causes it to darken. Its potency is affected in solutions of pH below 2 and is rapidly destroyed by alkali hydroxide solutions. Tetracycline is very slightly soluble in water, freely soluble in dilute acid and in alkali hydroxide solutions, sparingly soluble in alcohol, and practically insoluble in chloroform and ether.

Tetracycline hydrochloride is (4S,4aS,5aS,6S,12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride, with the following structural formula:



Molecular weight: 480.90

Inactive Ingredients: Each tetracycline hydrochloride capsule contains colloidal silicon dioxide, white ink, FD&C Red No. 40, gelatin, pregelatinized starch, stearic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Pharmacokinetics for the HELIDAC Therapy components (bismuth subsalicylate chewable tablets, metronidazole tablets, and tetracycline hydrochloride capsules) when coadministered has not been studied. There is no information about the gastric mucosal concentrations of bismuth, metronidazole, and tetracycline after administration of these agents concomitantly or in combination with an acid suppressive agent. The systemic pharmacokinetic information presented below is based on studies in which each product was administered alone.

Bismuth Subsalicylate: Upon oral administration, bismuth subsalicylate is almost completely hydrolyzed in the gastrointestinal tract to bismuth and salicylic acid. Thus, the pharmacokinetics of bismuth subsalicylate following oral administration can be described by the individual pharmacokinetics of bismuth and salicylic acid.

Bismuth: Less than 1% of bismuth from oral doses of bismuth subsalicylate is absorbed from the gastrointestinal tract into the systemic circulation. Absorbed bismuth is distributed throughout the body. Bismuth is highly bound to plasma proteins (> 90%). Bismuth has multiple disposition half-lives with an intermediate half-life of 5 to 11 days and a terminal half-life of 21 to 72 days. Elimination of bismuth is primarily through urinary and biliary routes with a renal clearance of 50 ± 18 mL/min. The mean trough blood bismuth concentration after 2 weeks oral administration of 787 mg bismuth subsalicylate (3 chewable tablets) four times daily under fasted condition was 5.1 ± 3.1 ng/mL. In another study, the mean trough blood bismuth concentration after 2 weeks oral administration of 525 mg bismuth subsalicylate (as PEPTO-BISMOL[®] liquid suspension) four times daily was 5 ng/mL with the highest value being 32 ng/mL.

Salicylic Acid: More than 80% of the salicylic acid is absorbed from oral doses of bismuth subsalicylate chewable tablets. Salicylic acid is about 90% plasma protein bound. The volume of distribution is about 170 mL/kg of body weight. Salicylic acid is extensively metabolized and about 10% is excreted unchanged in the urine. The metabolic clearance of salicylic acid is saturable; accordingly, nonlinear pharmacokinetics is observed at bismuth subsalicylate doses above 525 mg. Salicylic acid metabolic clearance is lower in females than in males. The terminal half-life of salicylic acid upon a single oral dose of 525 mg bismuth subsalicylate is between 2 to 5 hours. After a single oral dose of 525 mg bismuth subsalicylate (2 chewable tablets), the mean peak plasma salicylic acid concentration was 13.1 ± 3.4 µg/mL under fasted condition. The mean steady-state serum total salicylate concentration after 2 weeks oral administration of 525 mg bismuth subsalicylate (as PEPTO-BISMOL liquid suspension) four times daily was 24 µg/mL with the highest value being 70 µg/mL.

Metronidazole: Following oral administration, metronidazole is well absorbed, with peak plasma concentrations occurring between 1 and 2 hours after administration. Plasma concentrations of metronidazole are proportional to the administered dose, with oral administration of 250 mg producing a peak plasma concentration of 6 µg/mL. Studies reveal no significant bioavailability differences between males and females; however because of weight differences, the resulting plasma levels in males are generally lower.

Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Metronidazole also appears in cerebrospinal fluid, saliva, and human milk in concentrations similar to those found in plasma.

DRAFT

The average elimination half-life in normal volunteers is 8 hours. The major route of elimination of metronidazole and its metabolites is via the urine (60% to 80% of the dose), with fecal excretion accounting for 6% to 15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(β-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 mL/min/1.73 m².

DRAFT

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. In patients with decreased liver function, plasma clearance of metronidazole is decreased.

Tetracycline Hydrochloride: Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations in a biologically active form.

The relative contribution of systemic versus local antimicrobial activity against *H. pylori* for agents used in eradication therapy has not been established.

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*.~~

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.~~

DRAFT

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 methodology¹ and minimum inhibitory concentrations (MICs) were determined.

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 microaerobic growth conditions favored by *H. pylori*. Anaerobic pre-incubation decreases metronidazole MICs obtained when testing *H. pylori*.

DRAFT

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.

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 ($\leq 8 \mu\text{g/mL}$), 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 ($\geq 32 \mu\text{g/mL}$). Of the seven patients who had metronidazole resistant isolates pretreatment, 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)

| <u>Metronidazole Pretreatment Results</u> | | <u><i>H. pylori</i> negative (Eradicated)</u> | <u><i>H. pylori</i> positive (Not Eradicated) Post-treatment Metronidazole Results</u> | | |
|--|-----------|---|--|---------------------------------|---------------|
| | <u>N</u> | | <u>MIC ≤ 8</u> | <u>MIC ≥ 16</u> | <u>No MIC</u> |
| <u>MIC $\leq 8 \mu\text{g/mL}$</u> | <u>26</u> | <u>23</u> | <u>1</u> | <u>2</u> | <u>0</u> |
| <u>MIC $\geq 16 \mu\text{g/mL}$</u> | <u>7</u> | <u>4</u> | <u>1</u> | <u>1</u> | <u>1</u> |

^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.

Susceptibility Tests for *Helicobacter pylori*: The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.⁴ 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 |
|-----------------------------|---------------------|--------------------------|
| <i>H. pylori</i> 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.

INDICATIONS AND USAGE: The components of the HELIDAC Therapy (bismuth subsalicylate, metronidazole, and tetracycline hydrochloride), in combination with an H₂ antagonist, are indicated for the eradication of *H. pylori* for treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or a history of duodenal ulcer). Appropriate doses of H₂ antagonists for the treatment of active duodenal ulcers should be prescribed in all patients. The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence in patients with active duodenal ulcer disease. (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**.)

It is recommended that all patients not eradicated of *H. pylori* following HELIDAC Therapy plus an H₂ antagonist, should be considered to have *H. pylori* resistant to metronidazole retreated with a regimen which does not contain metronidazole. (See **Microbiology** subsection.)

CLINICAL STUDIES:

Eradication of *H. pylori* in Patients with Active Duodenal Ulcer Disease: Investigators in the U.S. (Graham et al., 1991, 1992, and Cutler et al., 1993) and Germany (Labenz et al., 1993) studied the effect of therapy on the eradication of *H. pylori* using bismuth subsalicylate, metronidazole, and tetracycline hydrochloride. The patient population in these studies consisted predominantly of duodenal ulcer patients with active disease. In addition to bismuth subsalicylate, metronidazole, tetracycline hydrochloride triple therapy, most patients were also prescribed antisecretory therapy at doses recommended for ulcer healing, with the majority receiving ranitidine. The primary efficacy variable used in these studies to determine effectiveness of therapy was *H. pylori* eradication, or cure of infection. Use of cure of infection as a surrogate for reduced ulcer recurrence is based on an extensive review of the literature. Eradication rates are derived from results of the randomized, controlled study of Graham et al. and the uncontrolled, nonrandomized study of Cutler et al. *H. pylori* eradication was defined as no positive test (culture, histology, rapid urease, or ¹³C breath test) at least 4 weeks following the end of treatment. In the analysis performed, dropouts and patients with missing *H. pylori* tests post-treatment were excluded. HELIDAC Therapy (bismuth subsalicylate, metronidazole, and tetracycline hydrochloride) was effective in eradicating *H. pylori*.

***Helicobacter pylori* Eradication Rates in Patients with Active Duodenal Ulcer Disease**

| Investigator | Eradication Rate in Duodenal Ulcer Patients [†] | 95% Confidence Intervals |
|-----------------------|--|--------------------------|
| Graham ^{2,3} | 77% (N = 39) | 61% - 89% |
| Cutler ⁴ | 82% (N = 51) | 70% - 92% |

[†] Evaluable patients were defined as having a confirmed duodenal ulcer within 2 years prior to treatment and having taken 14 days of bismuth subsalicylate, metronidazole, and tetracycline (range 11 to 17 days). Eradication was defined as no evidence of *H. pylori* infection by culture, histology, rapid urease test and/or urea breath test from at least 4 weeks post-treatment up to 1 year post-treatment.

Graham et al. 1992³ studied long-term outcome in patients treated for active duodenal ulcer by frequently monitoring for ulcer recurrence for up to 1 year after therapy. This study compared patients who received bismuth subsalicylate (BSS), metronidazole (MTZ), and tetracycline hydrochloride (TCN) for 2 weeks with ranitidine to those who received ranitidine alone. The ulcer recurrence rates at 6 months and 1 year regardless of post-treatment eradication status are summarized below for duodenal ulcer patients who were *H. pylori* positive at baseline.

Duodenal Ulcer Recurrence Rates at 6 Months[†]

| Therapy | All Patients | <i>H. pylori</i> Negative Patients Post-Treatment |
|--------------------------|--------------|---|
| BSS/MTZ/TCN + Ranitidine | 4% (1/25) | 6% (1/18) |
| Ranitidine | 85% (17/20) | 100% (1/1) |

Duodenal Ulcer Recurrence Rates at 1 Year[†]

| Therapy | All Patients | <i>H. pylori</i> Negative Patients Post-Treatment |
|--------------------------|--------------|---|
| BSS/MTZ/TCN + Ranitidine | 9% (2/22) | 13% (2/16) |
| Ranitidine | 95% (18/19) | 100% (1/1) |

[†] Includes all patients randomized to therapy who were *H. pylori* positive at baseline (by culture, histology, and/or urea breath test) who had ulcer healing and 24 or 48 weeks of endoscopic follow-up data.

Eradication of *H. pylori* in Patients with a History of Duodenal Ulcer Disease: A controlled, multicenter trial conducted by P&GP in the U.S. compared the rates of eradication of *H. pylori* following 14 days of treatment with HELIDAC Therapy (bismuth subsalicylate, metronidazole, and tetracycline hydrochloride) or control (bismuth subsalicylate, metronidazole placebo, and tetracycline placebo) in 103 patients infected with *H. pylori* who had a history of duodenal ulcer disease. No H₂-receptor antagonist was used. The primary efficacy measurement was *H. pylori* eradication assessed by rapid urease testing, histology, and culture at least 4 weeks after the last dose. HELIDAC Therapy was effective in eradicating *H. pylori*. The eradication rates are noted in the table below:

***H. pylori* Eradication Rates in Patients with a History of Duodenal Ulcer Disease**

| Population Therapy | Evaluable Population [†] | | Intent-To-Treat Population [‡] | |
|--|-----------------------------------|---------------------|---|---------------------|
| | HELIDAC Therapy | Control | HELIDAC Therapy | Control |
| Eradication Rate (Number of Patients) | 71% (40/56) | 7% (2/30) | 72% (41/57) | 6% (2/32) |
| 95% confidence interval | 60, 83 | 0 ^a , 16 | 60, 84 | 0 ^a , 15 |

^a The lower limit for this calculation was -2.2 but was truncated to 0 for reporting purposes.

[†] Evaluable patients were defined as having a history of a confirmed duodenal ulcer prior to treatment and having taken ≥ 70% of each component of HELIDAC Therapy (bismuth subsalicylate, metronidazole, tetracycline hydrochloride) during the 14-day dosing period. Eradication was defined as no evidence of *H. pylori* infection by two or three diagnostic tests (culture, histology, and rapid urease test) from at least 4 weeks to 6 weeks post-treatment. Excluded from the evaluable population were patients who were non-compliant with medication, patients who were not infected with *H. pylori* at baseline, and patients without ulcer documentation. Three patients in the HELIDAC Therapy group and one patient in the Control group were included as eradication failures because they withdrew from the study due to treatment-related adverse events.

[‡] Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodenal ulcer disease. All dropouts were included as failures of therapy. Eradication was defined as no evidence of *H. pylori* infection by culture, histology, or rapid urease test.

Compliance with the triple therapy regimen was also evaluated in the clinical study. In the intent-to-treat population, 93% of the HELIDAC Therapy group took at least 75% of their medication.

CONTRAINDICATIONS: This therapy is contraindicated in pregnant or nursing women, pediatric patients, in patients with renal or hepatic impairment, and in those with known hypersensitivity to bismuth subsalicylate, metronidazole or other nitroimidazole derivatives, or any of the tetracyclines. (See **WARNINGS** and **PRECAUTIONS**.) This product does not contain aspirin but should not be administered to those patients who have a known allergy to aspirin or salicylates.

WARNINGS

Bismuth Subsalicylate

Children and teenagers who have or who are recovering from chicken pox or flu should NOT use this medicine to treat nausea or vomiting. If nausea or vomiting is present, patients are advised to consult a doctor because this could be an early sign of Reye's syndrome, a rare but serious illness.

There have been rare reports of neurotoxicity associated with excessive doses of bismuth subsalicylate. Effects have been reversible with discontinuation of therapy.

Metronidazole

Central Nervous System Effects: Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The prevalence and severity of the neuropathy are directly related to the cumulative dose and duration of therapy, being most prevalent in patients taking high doses for prolonged treatment periods. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole therapy. Metronidazole should be administered with caution to patients with central nervous system diseases.

Pregnancy: Teratogenic Effects. Metronidazole crosses the placental barrier and its effects on the human fetal organogenesis are not known. No fetotoxicity was observed when metronidazole was administered orally to pregnant mice at 20 mg/kg/day approximately one and a half times the most frequently recommended human dose (750 mg/day) based on mg/kg body weight; however, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed. The relationship of these findings to the drug is unknown.

Tetracycline

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE HYDROCHLORIDE IS A COMPONENT OF THE HELIDAC THERAPY, THEREFORE, HELIDAC THERAPY SHOULD NOT BE USED IN THESE PATIENT POPULATIONS. (See **CONTRAINDICATIONS**.)

Tetracycline hydrochloride, as a component of the HELIDAC Therapy, should not be used during pregnancy. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs. Treatment should be discontinued at the first evidence of skin erythema.

The antianabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). While this is not a problem in those with normal renal function, in patients with significantly impaired renal function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis.

PRECAUTIONS

General:

Bismuth Subsalicylate

Bismuth subsalicylate may cause a temporary and harmless darkening of the tongue and/or black stool. Stool darkening should not be confused with melena.

Metronidazole

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in plasma. (See **CONTRAINDICATIONS**.) Metronidazole is a nitroimidazole and should be used with caution in patients with evidence of, or history of, blood dyscrasia. A mild leukopenia has been observed; however, no persistent hematologic abnormalities attributable to metronidazole have been observed.

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidicidal agent.

Tetracycline

As with other antibiotics, use of tetracycline hydrochloride may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, tetracycline should be discontinued and appropriate therapy should be instituted.

Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. While this condition and related symptoms usually resolve soon after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Information for Patients: Each dose includes 4 pills: 2 pink round chewable tablets (bismuth subsalicylate), 1 white round tablet (metronidazole), and 1 orange and white capsule (tetracycline hydrochloride). Each dose (all 4 pills) should be taken 4 times a day, at mealtimes and bedtime. Patients should be instructed to chew and swallow the pink round tablets (bismuth subsalicylate tablets) and to swallow the white round tablet (metronidazole tablet) and the pale orange and white capsule (tetracycline hydrochloride capsule) whole with a full glass of water (8 ounces). Concomitantly prescribed H₂ antagonist therapy should be taken as directed.

Administration of adequate amounts of fluid, particularly with the bedtime dose of tetracycline hydrochloride, is recommended to reduce the risk of esophageal irritation and ulceration. (See **ADVERSE REACTIONS**.)

Missed doses can be made up by continuing the normal dosing schedule until the medication is gone. Patients should not take double doses. (If more than 4 doses are missed, the prescriber should be contacted.)

This treatment regimen includes salicylates. If taken with aspirin and ringing in the ears occurs, the prescriber should be consulted concerning discontinuation of the aspirin therapy until the HELIDAC Therapy is completed.

Concurrent use of tetracyclines may render oral contraceptives less effective. Patients should be advised to use a different or additional form of contraception. Breakthrough bleeding has been reported. Women who become pregnant while taking components of the HELIDAC

Therapy should be advised to notify their prescriber immediately. (See **CONTRAINDICATIONS** and **WARNINGS**.)

Alcoholic beverages should be avoided while taking metronidazole and for at least 1 day afterward. (See **DRUG INTERACTIONS**.)

Patients taking tetracycline hydrochloride should be cautioned to avoid exposure to sun or sun lamps. (See **WARNINGS**.)

Bismuth subsalicylate may cause temporary and harmless darkening of the tongue and/or black stool. Stool darkening should not be confused with melena (blood in the stool).

Drug Interactions: Individual components of the HELIDAC Therapy have a potential interaction with anticoagulants. Tetracycline has been shown to depress plasma prothrombin activity. Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. Salicylates may cause an increased risk of bleeding when administered with anticoagulant therapy. Therefore, monitoring anticoagulant therapy with appropriate adjustment of the anticoagulant dosage may be warranted if concurrent therapy is instituted.

Caution is advised in the administration of bismuth subsalicylate to patients taking medication for diabetes (possible enhanced hypoglycemic effect when given with salicylates) or patients taking aspirin, probenecid, or sulfapyrazone.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium; preparations containing iron, zinc, or sodium bicarbonate; or milk or dairy products.

There is an anticipated reduction in tetracycline systemic absorption due to an interaction with bismuth and/or calcium carbonate, an excipient of bismuth subsalicylate tablets. The clinical significance of this is unknown as the relative contribution of systemic versus local antimicrobial activity against *H. pylori* for these agents has not been established.

Since bacteriostatic drugs, such as the tetracycline class of antibiotics, may interfere with the bactericidal action of penicillin, it is not advisable to administer these drugs concomitantly.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracycline may render oral contraceptives less effective. Patients should be advised to use a different or additional form of contraception. Breakthrough bleeding has been reported. Women who become pregnant while on the HELIDAC Therapy should be advised to notify their prescriber immediately.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole. The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

In patients stabilized on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity.

DRAFT
Serum lithium and serum creatinine should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

DRAFT
Alcoholic beverages should not be consumed during metronidazole therapy and for at least 1 day afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur.

DRAFT
Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

Drug/Laboratory Test Interactions: Bismuth absorbs x-rays and may interfere with x-ray diagnostic procedures of the gastrointestinal tract.

DRAFT
Bismuth subsalicylate may cause a temporary and harmless darkening of the stool. However, this does not interfere with standard tests for occult blood.

DRAFT
Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide ($\text{NAD}^+ \leftrightarrow \text{NADH}$). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats. Prominent among the effects in the mouse was an increased incidence of pulmonary tumorigenesis. This has been observed in all six reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). At very high dose levels, (approximately 500 mg/kg/day, which is approximately 33 times the most frequently recommended human dose for a 50 kg adult based on mg/kg body weight), there was a statistically significant increase in the incidence of malignant liver tumors in male mice. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant. Long-term, oral-dosing studies in the rat showed statistically significant increases in the incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

DRAFT
There has been no evidence of carcinogenicity for tetracycline hydrochloride in studies conducted with rats and mice. Some related antibiotics (oxytetracycline, minocycline) have shown evidence of oncogenic activity in rats.

No long-term toxicity studies have been conducted with bismuth subsalicylate.

DRAFT
No long-term studies have been performed to evaluate the effect of the combined use of bismuth subsalicylate, metronidazole, and tetracycline on carcinogenesis, mutagenesis, or impairment of fertility.

DRAFT
Although metronidazole has shown mutagenic activity in a number of *in vitro* assay systems, studies in mammals (*in vivo*) have failed to demonstrate a potential for genetic damage.

ADVERSE REACTIONS: The most common adverse reactions ($\geq 1\%$) reported in clinical trials when all three components of this therapy were given concomitantly are listed in the table below. The majority of the adverse reactions were related to the gastrointestinal tract, were reversible, and infrequently led to discontinuation of therapy.

Incidence of Adverse Reactions Reported in Clinical Trials ($\geq 1\%$)[†]

| Adverse Reactions | BSS/MTZ/TCN[‡] (N = 266) % Patients |
|-----------------------------|---|
| Nausea | 12 |
| Diarrhea | 6.8 |
| Abdominal Pain | 6.8 |
| Melena | 3 |
| Upper Respiratory Infection | 2.3 |
| Constipation | 1.9 |
| Anorexia | 1.5 |
| Asthenia | 1.5 |
| Vomiting | 1.5 |
| Discolored Tongue | 1.5 |
| Headache | 1.5 |
| Dyspepsia | 1.5 |
| Dizziness | 1.5 |
| Stool Abnormality | 1.1 |
| Duodenal Ulcer | 1.1 |
| Sinusitis | 1.1 |
| Taste Perversion | 1.1 |
| Flatulence | 1.1 |
| GI Hemorrhage | 1.1 |
| Pain | 1.1 |
| Insomnia | 1.1 |
| Anal Discomfort | 1.1 |
| Paresthesia | 1.1 |

[†] Includes reactions reported at $\geq 1\%$ in patients taking BSS/MTZ/TCN in Graham, Cutler, and P&GP studies.

[‡] In the Graham and Cutler studies (N = 197), most patients were on concomitant acid suppression therapy.

The additional adverse reactions (< 1%) reported in clinical trials when all three components of this therapy were given concomitantly are listed below and divided by body system:

Gastrointestinal: dry mouth, dysphagia, eructation, GI monilia, glossitis, intestinal obstruction, rectal hemorrhage, stomatitis

Skin: acne, ecchymosis, photosensitivity reaction (see **WARNINGS**), pruritus, rash

Cardiovascular: cerebral ischemia, chest pain, hypertension, myocardial infarction

CNS: nervousness, somnolence

Musculoskeletal: arthritis, rheumatoid arthritis, tendonitis

Metabolic: SGOT increase, SGPT increase

Urogenital: urinary tract infection

Other: conjunctivitis, flu syndrome, infection, malaise, neoplasm, rhinitis, syncope, tooth disorder

The following adverse reactions from the labeling for bismuth subsalicylate are provided for information.

Gastrointestinal: black stools

Mouth: temporary and harmless darkening of the tongue

The following adverse reactions from the labeling for metronidazole are provided for information.

Gastrointestinal: The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea reported by about 12% of patients, sometimes accompanied by headache, anorexia, and occasionally vomiting, diarrhea, epigastric distress, and abdominal cramping. Constipation has also been reported.

Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during therapy.

Blood: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

CNS: Convulsive seizures, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness, and insomnia. Two serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur.

Hypersensitivity: urticaria, erythematous rash, flushing, nasal congestion, dryness of mouth (or vagina or vulva), and fever

Renal: Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately one patient in 100,000. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

Other: Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing, or headache. A modification of the taste of alcoholic beverages has also been reported. Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported.

The following adverse reactions from the labeling for tetracycline hydrochloride are provided for information.

Gastrointestinal: Anorexia, nausea, epigastric distress, vomiting, diarrhea, glossitis, black hairy tongue, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Rare instances of esophagitis and esophageal

ulceration have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of the patients who experienced esophageal irritation took the medication immediately before going to bed. (See **DOSAGE AND ADMINISTRATION.**)

Liver: Hepatotoxicity and liver failure have been observed in patients receiving large doses of tetracycline and in tetracycline-treated patients with renal impairment. Increases in liver enzymes and hepatic toxicity have been reported rarely.

Teeth: Permanent discoloration of teeth may be caused during tooth development. Enamel hypoplasia has also been reported. (See **WARNINGS.**)

Blood: hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, neutropenia, and eosinophilia

CNS: Pseudotumor cerebri (benign intracranial hypertension) in adults and bulging fontanels in infants. (See **PRECAUTIONS: Tetracycline.**) Dizziness, tinnitus, and visual disturbances have been reported. Myasthenic syndrome has been reported rarely.

Hypersensitivity: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus and serum sickness-like reactions, as fever, rash, and arthralgia

Renal: Rise in BUN has been reported and is apparently dose related. (See **WARNINGS.**)

Skin: Maculopapular and erythematous rashes have been reported. Exfoliative dermatitis has been rarely reported. Photosensitivity (see **WARNINGS**), onycholysis, and discoloration of the nails have been reported rarely.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

OVERDOSAGE: In case of an overdose, patients should contact a physician, poison control center, or emergency room. If all three components of this therapy are involved in an overdose, acute treatment should focus on the salicylate intoxication. There is neither a pharmacologic basis nor data suggesting an increased toxicity of the combination compared to individual components.

Bismuth Subsalicylate: The main concern of an acute bismuth subsalicylate (BSS) overdose focuses on the salicylate burden and not on bismuth, since less than 1% of the bismuth is normally absorbed. Each 262.4-mg tablet of BSS contains an amount of salicylate comparable to approximately 130 mg aspirin. Acute ingestion of less than 150 mg/kg of aspirin (i.e., less than one tablet of bismuth subsalicylate per kilogram of body weight) is not expected to lead to toxicity. Mild to moderate toxicity may result from the ingestion of 150 to 300 mg/kg, while severe toxicity may occur from ingestions over 300 mg/kg. Salicylate intoxication is well described in the literature and presents a complex clinical picture. Multiple respiratory and metabolic effects result in fluid, electrolyte, glucose, and acid-base disturbances. Initial symptoms of salicylate toxicity include hyperpnea, nausea, vomiting, tinnitus, hyperpyrexia, lethargy, tachycardia, and confusion. In severe cases, these symptoms may progress to severe hyperpnea, convulsions, pulmonary or cerebral edema, respiratory failure, cardiovascular collapse, coma, and death.

Treatment: There is no specific antidote for salicylate poisoning. If there are no contraindications, vomiting should be induced as soon as possible with syrup of ipecac, or gastric lavage should be instituted, provided that no more than one hour has elapsed since ingestion. Activated charcoal and a cathartic may be administered as primary decontamination

DRAFT
DRAFT
DRAFT
DRAFT
DRAFT

therapy in those cases where greater than one hour has elapsed since ingestion, or to further decontaminate the gastrointestinal tract in those who have already received ipecac or gastric lavage. Plasma salicylate levels may be useful; a common nomogram can be used to help predict the severity of intoxication. Supportive and symptomatic treatment should be provided, with emphasis on correcting fluid, electrolyte, blood glucose, and acid-base disturbances. (Note: An acidotic blood pH increases the un-ionized salicylate form, allowing more to reach the central nervous system.) Elimination may be enhanced by urinary alkalinization, hemodialysis, or hemoperfusion. Since hemodialysis aids in correcting acid-base disturbances, this method may be preferred over hemoperfusion.

Metronidazole: Single oral doses of metronidazole, up to 19.5 g in adults, have been reported without resultant serious toxicity in suicide attempts and accidental overdoses. Symptoms reported include nausea, vomiting, and ataxia.

Neurotoxic effects, including seizures and peripheral neuropathy, have been reported after 5 to 7 days of doses of 6 to 10.4 g every other day.

Treatment: There is no specific antidote for metronidazole overdose. Management of the patient should consist of symptomatic and supportive therapy. Metronidazole is dialyzable.

Tetracycline: The acute toxicity of tetracycline in overdose is not well established in the literature. Therapeutic and overdose quantities of tetracycline can cause gastrointestinal symptoms such as nausea, vomiting, and diarrhea.

Treatment: There is no specific antidote for tetracycline overdose. Management of the patient should consist of symptomatic and supportive therapy. Tetracycline is not dialyzable.

DOSAGE AND ADMINISTRATION: Adults: The recommended dosages are: bismuth subsalicylate, 525 mg (two 262.4 mg-chewable tablets), metronidazole, 250 mg (one 250-mg tablet), and tetracycline hydrochloride, 500 mg (one 500-mg capsule) taken four times daily (q.i.d.) for 14 days plus an H₂ antagonist approved for the treatment of acute duodenal ulcer. Patients should be instructed to take the medicines at mealtimes and at bedtime. The bismuth subsalicylate tablets should be chewed and swallowed. The metronidazole tablet and tetracycline hydrochloride capsule should be swallowed whole with a full glass of water (8 ounces). Concomitantly prescribed H₂ antagonist therapy should be taken as directed.

Ingestion of adequate amounts of fluid, particularly with the bedtime dose of tetracycline hydrochloride, is recommended to reduce the risk of esophageal irritation and ulceration. (See **ADVERSE REACTIONS.**)

Missed doses can be made up by continuing the normal dosing schedule until the medication is gone. Patients should not take double doses. If more than 4 doses are missed, the prescriber should be contacted.

DRAFT
DRAFT
DRAFT
DRAFT

HOW SUPPLIED: The HELIDAC Therapy is supplied in a carton containing patient instructions, patient reminders, and 14 blister cards, each card containing the following daily dosage:

8 bismuth subsalicylate 262.4-mg chewable tablets, each pink round tablet engraved "PG 11"

4 metronidazole 250-mg tablets, each white round tablet engraved "PG" on the upper half and "10" on the lower half of the tablet

4 tetracycline hydrochloride 500-mg capsules, each pale orange and white capsule printed "PG 12" in white ink

NDC 0149-0495-01 carton containing 14 days of therapy

Store at controlled room temperature 20°-25°C (68°-77°F) [See USP].

REFERENCES:

- ~~1. National Committee for Clinical Laboratory Standards. Summary Minutes, Subcommittee on Antimicrobial Susceptibility Testing, Tampa, FL. January, 1997.~~
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.
2. Graham DY, Lew GM, Evans DG, Evans DJ Jr, Klein PD. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. *Ann Intern Med* 1991; 115:266-69.
3. Graham DY, Lew GM, Klein PD, Evans DG, Evans DJ Jr, Saeed ZA, Malaty HM. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. *Ann Int Med* 1992; 116:705-08.
4. Cutler AF, Schubert TT. Long-term *Helicobacter pylori* recurrence after successful eradication with triple therapy. *Am J Gastroenterol* 1993; 88:1359-61.

Sold under U.S. Patents 5,256,684; 5,403,830; 5,407,688; and 5,601,848

PEPTO-BISMOL is the registered trademark of The Procter & Gamble Company.

Bismuth subsalicylate tablets are manufactured by Procter & Gamble Pharmaceuticals. Metronidazole 250-mg tablets, USP and tetracycline hydrochloride 500-mg capsules, USP are manufactured by Zenith Laboratories, Inc., Northvale, New Jersey 07647 for

Procter & Gamble Pharmaceuticals
Cincinnati, Ohio 45202

REVISED JUNE 1999