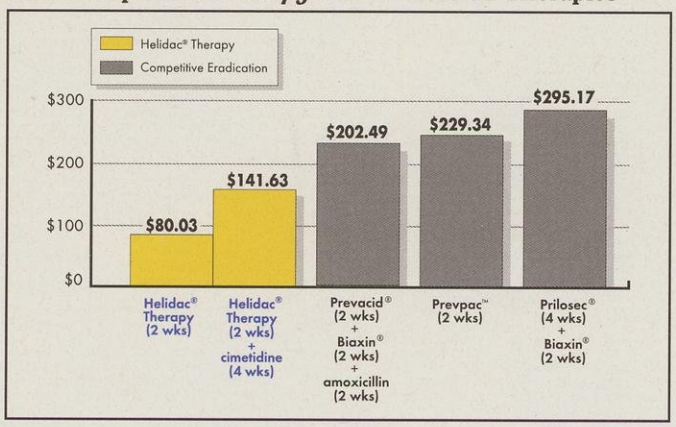
Helidac Therapy advertisement.

[s.l.]: [s.n.], 1997

Without burying their budgets.

Helidac® Therapy with an H_2 antagonist eradicates *H. pylori* at a cost up to 50% lower than other eradication therapy brands.†

Cost Comparison of *H. pylori* Eradication Therapies†



Helidac Therapy is well tolerated, allowing at least 96% of patients to complete the therapy in clinical studies; most common side effects include nausea (10%), diarrhea (5%), and abdominal pain (3%). Patients who fail treatment should not be retreated with a regimen containing metronidazole. Helidac Therapy is contraindicated in pregnant or nursing women, pediatric patients, patients with renal or hepatic impairment and in patients with hypersensitivity to any of the components of Helidac Therapy or related compounds.

Efficacy: At one year among all evaluable patients, in combination with an H_2 antagonist, Helidac® Therapy achieved

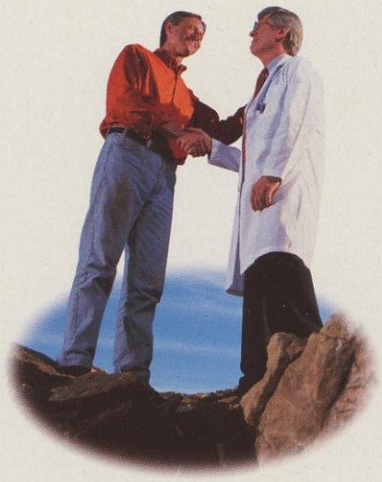
- 91% no ulcer recurrence
- *H. pylori* eradication rates up to 82%

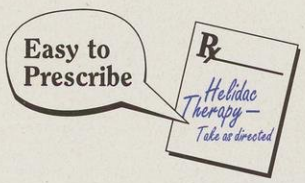
Compliance:

- 95% of all patients took at least 95% of Helidac Therapy*

Convenient Packaging:

- 14 blister cards, patient information booklet, daily reminder notes





Helidac® Therapy
(bismuth subsalicylate/metronidazole/tetracycline hydrochloride)

Power and Compliance: An Ulcer-Ending Alliance.

† Lowest cost eradication therapy claim is valid versus all therapies indicated for the eradication of *H. pylori* in active duodenal ulcers. Costs are AWP from Red Book, June, 1998. Helidac Therapy AWP = $80.03. Lower acquisition cost alone does not necessarily reflect a cost advantage. Products that are subject of a price comparison are not known to have comparable efficacy. The referenced prices (derived from published price lists) do not necessarily reflect actual prices paid by consumers or dispensers.

Cost comparison is valid with respect to branded therapies when prescribed exclusively for the treatment of active duodenal ulcers associated with *H. pylori* infection. Prilosec, Prevacid, Biaxin, Prevpac, and amoxicillin have additional indications.

* P&GP data on file.

Prilosec® (omeprazole) is a registered trademark of Astra Aktiebolag. Biaxin® (clarithromycin) is a registered trademark of Abbott Laboratories. Prevpac™ (lansoprazole/amoxicillin/clarithromycin) is a trademark of TAP Pharmaceuticals, Inc. Prevacid® (lansoprazole) is a registered trademark of TAP Pharmaceuticals, Inc.

Please see accompanying brief summary of prescribing information. HL978-71,80

Helidac® Therapy

(bismuth subsalicylate/metronidazole/tetracycline hydrochloride)

Power and Compliance: An Ulcer-Ending Alliance.

HELIDAC® Therapy

(bismuth subsalicylate/metronidazole/tetracycline hydrochloride)

BRIEF SUMMARY: (For full prescribing information, see package insert.)

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.

INDICATIONS AND USAGE: The components of the HELIDAC Therapy (bismuth subsalicylate, metronidazole, and tetracycline hydrochloride), in combination with an H_2 antagonist are indicated for the treatment of patients with an active duodenal ulcer associated with *Helicobacter pylori* infection. The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence. Appropriate doses of H_2 antagonists for the treatment of active duodenal ulcers should be prescribed for ulcer healing. (See **DOSAGE AND ADMINISTRATION**.) It is recommended that all patients not eradicated of *Helicobacter pylori* following HELIDAC Therapy plus an H_2 antagonist should be considered to have *Helicobacter pylori* resistant to metronidazole. Patients who fail therapy should not be retreated with a regimen containing metronidazole.

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 anti-anabolic 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 the 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 candicidal agent. **Tetracycline:** As with other antibiotics, use of tetracycline hydrochloride may result in overgrowth of non-susceptible 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:** See full prescribing information for **Information for Patients. 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 sulfinpyrazone. 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. 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. 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. 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. Bismuth subsalicylate may cause a temporary and harmless darkening of the stool. However, this does not interfere with standard tests for occult blood. 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 (NAD^+ ¤ 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. 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. 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. 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. In two *in vitro* mammalian cell assay systems (L51784y mouse lymphoma and Chinese hamster lung cells), there was evidence of mutagenicity by tetracycline hydrochloride at concentrations of 60 and 10 µg/mL, respectively. Bismuth did not show mutagenic potential in the NTP salmonella plate assay. No reproductive toxicity studies have been conducted with bismuth subsalicylate. Tetracycline hydrochloride had no effect on fertility when administered in the diet to male and female rats at a daily intake of 25 times the human dose. Metronidazole, at doses up to 400 mg/kg/day (approximately 3.5 times the recommended maximum human dose based on mg/m^2) for 28 days, failed to produce any adverse effects on fertility and testicular function in male rats. Fertility studies have been performed in mice at doses up to six times the maximum recommended human dose based on mg/m^2 and have revealed no evidence of impaired fertility. **Pregnancy: Teratogenic Effects. Pregnancy Category D:** Category D is based on the pregnancy category for tetracycline hydrochloride. (See **CONTRAINDICATIONS** and **WARNINGS, Tetracycline** and **Metronidazole** subsections.) **Non-teratogenic Effects:** (See **WARNINGS**.) Pregnant women with renal disease may be more prone to develop tetracycline-associated liver failure. **Labor and Delivery:** The effect of this therapy on labor and delivery is unknown. **Nursing Mothers:** Metronidazole and tetracycline are both secreted into human milk. Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, and because of the potential for serious adverse reactions in nursing infants from tetracyclines, a decision should be made whether to discontinue nursing or to discontinue therapy, taking into account the importance of the therapy to the mother. Metronidazole is secreted in human milk in concentrations similar to those found in plasma. (See **CONTRAINDICATIONS**.) **Pediatric Use:** Safety and effectiveness in pediatric patients infected with *H. pylori* have not been established. (See **CONTRAINDICATIONS** and **WARNINGS**.) **Geriatric Use:** Elderly patients may suffer from asymptomatic renal and hepatic dysfunction. Care should be taken when administering this therapy to this patient population.

ADVERSE REACTIONS: The majority of the adverse reactions were related to the gastrointestinal tract, were reversible, and infrequently led to discontinuation of therapy. The most common adverse reactions reported in clinical trials when all three components of this therapy were given concomitantly (includes reactions reported at ≥1.0% in patients taking BSS/MTZ/TCN, most of whom were on concomitant acid suppression therapy) were, for BSS/MTZ/TCN patients (n = 197) and ranitidine patients (n = 73), respectively: nausea, 10.2%, 1.4%; diarrhea, 5.1%, 0.0%; abdominal pain, 3.0%, 0.0%; melena, 2.5%, 0.0%; anal discomfort, 1.5%, 0.0%; anorexia, 1.5%, 0.0%; dizziness, 1.5%, 0.0%; paresthesia, 1.5%, 0.0%; vomiting, 1.5%, 0.0%; asthenia, 1.0%, 0.0%; constipation, 1.0%, 0.0%; insomnia, 1.0%, 0.0%; pain, 1.0%, 0.0%; and upper respiratory infection, 1.0%, 0.0%.

HELIDAC® Therapy (bismuth subsalicylate/metronidazole/tetracycline hydrochloride)

The additional adverse reactions (<1%) reported in clinical trials when all three components of this therapy were given concomitantly divided by body system were: **Gastrointestinal:** dry mouth, dyspepsia, dysphagia, flatulence, gastrointestinal hemorrhage, glossitis, stomatitis; **Skin:** photosensitivity reaction (see **WARNINGS**), rash; **Cardiovascular:** hypertension, myocardial infarction; **CNS:** nervousness; **Musculoskeletal:** rheumatoid arthritis; **Other:** malaise, syncope.
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** subsection.) 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. **See full prescribing information for additional information on overdosage with the components of Helidac Therapy.**

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 H_2 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 H_2 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.

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

CAUTION: Federal law prohibits dispensing without prescription.

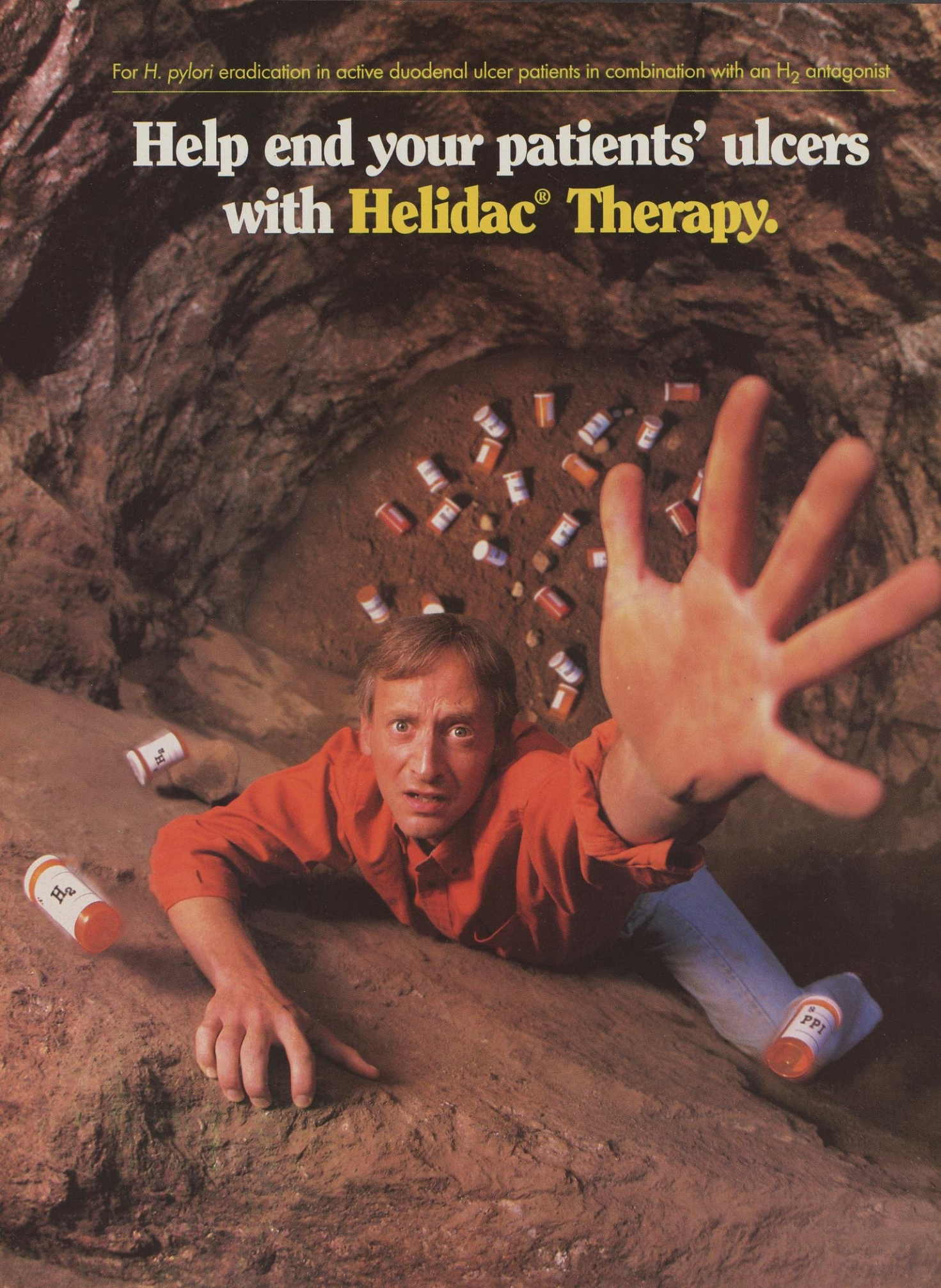
Sold Under U.S. Patent No. 5,256,684

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 AUGUST 1997

For *H. pylori* eradication in active duodenal ulcer patients in combination with an H_2 antagonist

Help end your patients' ulcers with Helidac® Therapy.



Without burying their budgets.

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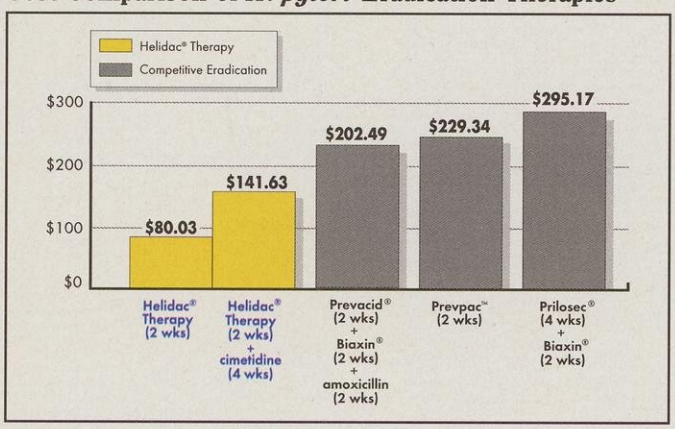
Cost Comparison of *H. pylori* Eradication Therapies†



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- 91% no ulcer recurrence
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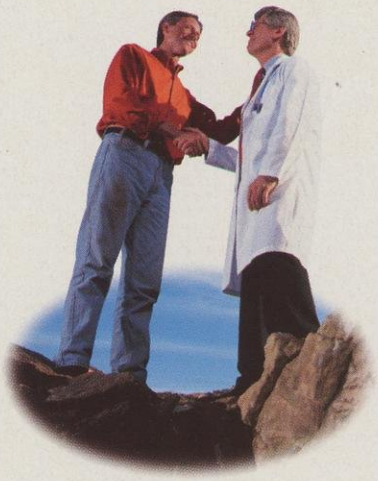

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INDICATIONS AND USAGE: The components of the HELIDAC Therapy (bismuth subsalicylate, metronidazole, and tetracycline hydrochloride), in combination with an H_2 antagonist are indicated for the treatment of patients with an active duodenal ulcer associated with *Helicobacter pylori* infection. The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence. Appropriate doses of H_2 antagonists for the treatment of active duodenal ulcers should be prescribed for ulcer healing. (See **DOSAGE AND ADMINISTRATION**.) It is recommended that all patients not eradicated of *Helicobacter pylori* following HELIDAC Therapy plus an H_2 antagonist should be considered to have *Helicobacter pylori* resistant to metronidazole. Patients who fail therapy should not be retreated with a regimen containing metronidazole.

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 anti-anabolic 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 the 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 candicidal agent. **Tetracycline:** As with other antibiotics, use of tetracycline hydrochloride may result in overgrowth of non-susceptible 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:** See full prescribing information for **Information for Patients. 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 sulfinpyrazone. 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. 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. 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. 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. Bismuth subsalicylate may cause a temporary and harmless darkening of the stool. However, this does not interfere with standard tests for occult blood. 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 (NAD^+ ⇌ 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. 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. 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. 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. In two *in vitro* mammalian cell assay systems (L51784y mouse lymphoma and Chinese hamster lung cells), there was evidence of mutagenicity by tetracycline hydrochloride at concentrations of 60 and 10 µg/mL, respectively. Bismuth did not show mutagenic potential in the NTP salmonella plate assay. No reproductive toxicity studies have been conducted with bismuth subsalicylate. Tetracycline hydrochloride had no effect on fertility when administered in the diet to male and female rats at a daily intake of 25 times the human dose. Metronidazole, at doses up to 400 mg/kg/day (approximately 3.5 times the recommended maximum human dose based on mg/m^2) for 28 days, failed to produce any adverse effects on fertility and testicular function in male rats. Fertility studies have been performed in mice at doses up to six times the maximum recommended human dose based on mg/m^2 and have revealed no evidence of impaired fertility.
Pregnancy: Teratogenic Effects. Pregnancy Category D: Category D is based on the pregnancy category for tetracycline hydrochloride. (See **CONTRAINDICATIONS** and **WARNINGS, Tetracycline** and **Metronidazole** subsections.) **Non-teratogenic Effects:** (See **WARNINGS**.) Pregnant women with renal disease may be more prone to develop tetracycline-associated liver failure. **Labor and Delivery:** The effect of this therapy on labor and delivery is unknown. **Nursing Mothers:** Metronidazole and tetracycline are both secreted into human milk. Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, and because of the potential for serious adverse reactions in nursing infants from tetracyclines, a decision should be made whether to discontinue nursing or to discontinue therapy, taking into account the importance of the therapy to the mother. Metronidazole is secreted in human milk in concentrations similar to those found in plasma. (See **CONTRAINDICATIONS**.)
Pediatric Use: Safety and effectiveness in pediatric patients infected with *H. pylori* have not been established. (See **CONTRAINDICATIONS** and **WARNINGS**.)
Geriatric Use: Elderly patients may suffer from asymptomatic renal and hepatic dysfunction. Care should be taken when administering this therapy to this patient population.

ADVERSE REACTIONS: The majority of the adverse reactions were related to the gastrointestinal tract, were reversible, and infrequently led to discontinuation of therapy. The most common adverse reactions reported in clinical trials when all three components of this therapy were given concomitantly (includes reactions reported at ≥1.0% in patients taking BSS/MTZ/TCN, most of whom were on concomitant acid suppression therapy) were, for BSS/MTZ/TCN patients (n = 197) and ranitidine patients (n = 73), respectively: nausea, 10.2%, 1.4%; diarrhea, 5.1%, 0.0%; abdominal pain, 3.0%, 0.0%; melena, 2.5%, 0.0%; anal discomfort, 1.5%, 0.0%; anorexia, 1.5%, 0.0%; dizziness, 1.5%, 0.0%; paresthesia, 1.5%, 0.0%; vomiting, 1.5%, 0.0%; asthenia, 1.0%, 0.0%; constipation, 1.0%, 0.0%; insomnia, 1.0%, 0.0%; pain, 1.0%, 0.0%; and upper respiratory infection, 1.0%, 0.0%.

HELIDAC® Therapy (bismuth subsalicylate/metronidazole/tetracycline hydrochloride)

The additional adverse reactions (<1%) reported in clinical trials when all three components of this therapy were given concomitantly divided by body system were: **Gastrointestinal:** dry mouth, dyspepsia, dysphagia, flatulence, gastrointestinal hemorrhage, glossitis, stomatitis; **Skin:** photosensitivity reaction (see **WARNINGS**), rash; **Cardiovascular:** hypertension, myocardial infarction; **CNS:** nervousness; **Musculoskeletal:** rheumatoid arthritis; **Other:** malaise, syncope.
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 moniliai 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** subsection.) 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. **See full prescribing information for additional information on overdosage with the components of Helidac Therapy.**

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 H_2 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 H_2 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.

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

CAUTION: Federal law prohibits dispensing without prescription.

Sold Under U.S. Patent No. 5,256,684

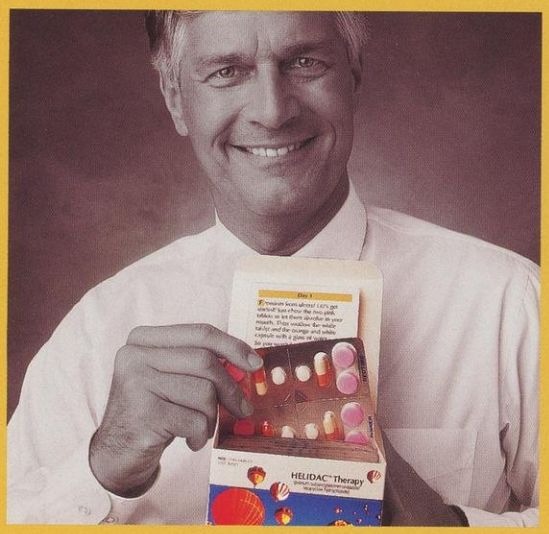
PEPTO-BISMOL is the registered trademark of The Procter & Gamble Company. Bismuth subsalicylate tablets are manufactured by Procter & Gamble Pharmaceuticals. Metronidazole 250-mg tablets, USP and tetracycline hydrochloride 500-mg capsules. USP are manufactured by Zenith Laboratories, Inc., Northvale, New Jersey 07647 for **Procter & Gamble Pharmaceuticals**, Cincinnati, Ohio 45202.

REVISED AUGUST 1997

For *H. pylori* eradication in active duodenal ulcer patients in combination with an H_2 antagonist

NEW

Finally, Powerful Triple Therapy Any Patient Can Grasp



Daily Dosage Cards

Patient Education

Highly effective

At 1 year among **all** evaluable patients, HELIDAC Therapy with an H_2 antagonist achieved:
— *H. pylori* eradication rates of up to 82%
— 91% of **all** patients had no ulcer recurrence

Designed for compliance

Patients prefer HELIDAC Therapy's convenient packaging versus three individually dispensed drugs.*

Well tolerated

HELIDAC Therapy is well tolerated; most common side effects include nausea (10%), diarrhea (5%) and abdominal pain (3%).

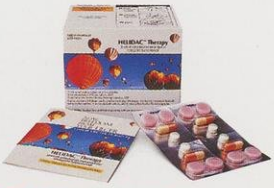
Patients who fail therapy should not be retreated with a regimen containing metronidazole.

HELIDAC Therapy is contraindicated in pregnant or nursing women, pediatric patients and patients with renal or hepatic impairment.

Rx
HELIDAC—
Take as directed

Helidac™ Therapy

(bismuth subsalicylate/metronidazole/tetracycline hydrochloride)



POWERFUL TRIPLE THERAPY THAT'S DESIGNED FOR COMPLIANCE

*P&GP, data on file.

Please see brief summary of prescribing information on following page.

Helidac™ Therapy

(bismuth subsalicylate/metronidazole/tetracycline hydrochloride)

POWERFUL TRIPLE THERAPY THAT'S DESIGNED FOR COMPLIANCE

HELIDAC™ Therapy

(bismuth subsalicylate/metronidazole/tetracycline hydrochloride)

BRIEF SUMMARY: (For full Prescribing Information, see package insert.)

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.

INDICATIONS AND USAGE: The components of the HELIDAC Therapy (bismuth subsalicylate, metronidazole, and tetracycline hydrochloride), in combination with an H_2 antagonist are indicated for the treatment of patients with an active duodenal ulcer associated with *Helicobacter pylori* infection. The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence. Appropriate doses of H_2 antagonists for the treatment of active duodenal ulcers should be prescribed for ulcer healing. (See **DOSAGE AND ADMINISTRATION**.) It is recommended that all patients not eradicated of *Helicobacter pylori* following HELIDAC Therapy plus an H_2 antagonist should be considered to have *Helicobacter pylori* resistant to metronidazole. Patients who fail therapy should not be retreated with a regimen containing metronidazole.

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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. 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. 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. 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. Bismuth subsalicylate may cause a temporary and harmless darkening of the stool. However, this does not interfere with standard tests for occult blood. 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 nicotine adenine dinucleotide (NAD^+ ⇄ 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, 500 mg/kg/day, (approximately $\frac{1}{2}$ two times the recommended maximum human dose based on mg/m^2), 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. 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. 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. 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. In two *in vitro* mammalian cell assay systems (L51784y mouse lymphoma and Chinese hamster lung cells), there was evidence of mutagenicity by tetracycline hydrochloride at concentrations of 60 and 10 μg/mL, respectively. Bismuth did not show mutagenic potential in the NTP salmonella plate assay. No reproductive toxicity studies have been conducted with bismuth subsalicylate. Tetracycline hydrochloride had no effect on fertility when administered in the diet to male and female rats at a daily intake of 25 times the human dose. Metronidazole, at doses up to 400 mg/kg/day (approximately 3.5 times the recommended maximum human dose based on mg/m^2) for 28 days, failed to produce any adverse effects on fertility and testicular function in male rats.
Pregnancy: Teratogenic Effects. Pregnancy Category D: Category D is based on the pregnancy category for tetracycline hydrochloride. (See **CONTRAINDICATIONS** and **WARNINGS**, **Tetracycline** subsection.)
Non-teratogenic Effects: (See **WARNINGS**.) Pregnant women with renal disease may be more prone to develop tetracycline-associated liver failure. **Labor and Delivery:** The effect of this therapy on labor and delivery is unknown. **Nursing Women:** Metronidazole and tetracycline are both secreted into human milk. Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, and because of the potential for serious adverse reactions in nursing infants from tetracyclines, a decision should be made whether to discontinue nursing or to discontinue therapy, taking into account the importance of the therapy to the mother. Metronidazole is secreted in human milk in concentrations similar to those found in plasma. (See **CONTRAINDICATIONS**.)
Pediatric Use: Safety and effectiveness in pediatric patients infected with *H. pylori* have not been established. (See **CONTRAINDICATIONS** and **WARNINGS**.)
Geriatric Use: Elderly patients may suffer from asymptomatic renal and hepatic dysfunction. Care should be taken when administering this therapy to this patient population.

ADVERSE REACTIONS: The majority of the adverse reactions were related to the gastrointestinal tract, were reversible, and infrequently led to discontinuation of therapy. The most common adverse reactions reported in clinical trials when all three components of this therapy were given concomitantly (includes reactions reported at ≥1.0% in patients taking BSS/MTZ/TCN, most of whom were on concomitant acid suppression therapy) were, for BSS/MTZ/TCN patients (n = 197) and ranitidine patients (n = 73), respectively: nausea, 0.2%, 0.4%; diarrhea, 5.1%, 0.0%; abdominal pain, 3.0%, 0.0%; melena, 2.5%, 0.0%; anal discomfort, 1.5%, 0.0%; anorexia, 1.5%, 0.0%; dizziness, 1.5%, 0.0%; paresthesia, 1.5%, 0.0%; vomiting, 1.5%, 0.0%; asthenia, 1.0%, 0.0%; constipation, 1.0%, 0.0%; insomnia, 1.0%, 0.0%; pain, 1.0%, 0.0%; and upper respiratory infection, 1.0%, 0.0%.
The additional adverse reactions (<1%) reported in clinical trials when all three components of this therapy were given concomitantly divided by body system were: **Gastrointestinal:** dry mouth, dyspepsia, dysphagia, flatulence, gastrointestinal hemorrhage, glossitis, stomatitis; **Skin:** photosensitivity reaction (see **WARNINGS**), rash; **Cardiovascular:** hypertension, myocardial infarction; **CNS:** nervousness; **Musculoskeletal:** rheumatoid arthritis; **Other:** malaise, syncope.
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** subsection.) 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. **See full prescribing information for additional information on overdosage with the components of Helidac Therapy.**

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 H_2 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 H_2 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.

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

CAUTION: Federal law prohibits dispensing without prescription.

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