

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PYLERA safely and effectively. See full prescribing information for PYLERA

PYLERA® (bismuth subcitrate potassium, metronidazole, tetracycline hydrochloride) capsules, for oral use
Initial U.S. Approval: 2006

WARNING: POTENTIAL FOR CARCINOGENICITY
See full prescribing information for complete boxed warning

Metronidazole has been shown to be carcinogenic in mice and rats. It is unknown whether metronidazole is associated with carcinogenicity in humans (5.1).

RECENT MAJOR CHANGES

| | |
|------------------------------|--------|
| Boxed Warning | 1/2017 |
| Contraindications (4) | 1/2017 |
| Warnings and Precautions (5) | 5/2017 |

INDICATIONS AND USAGE

PYLERA is a combination of metronidazole, a nitroimidazole antimicrobial, tetracycline, a tetracycline class antimicrobial and bismuth subcitrate potassium, indicated for use, in combination with omeprazole, for the treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. (1.1)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of PYLERA and other antibacterial drugs, PYLERA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.2)

DOSAGE AND ADMINISTRATION

- Administer three PYLERA capsules 4 times a day (after meals and at bedtime) for 10 days. (2)
- Administer PYLERA with omeprazole 20 mg twice daily (after the morning and evening meals). (2)

DOSAGE FORMS AND STRENGTHS

Each capsule of PYLERA contains: (3)

- 140 mg of bismuth subcitrate potassium
- 125 mg metronidazole
- 125 mg of tetracycline hydrochloride

CONTRAINDICATIONS

- Concurrent usage of Methoxyflurane. (4.1, 7.1)
- Disulfiram usage within the last two weeks. (4.2, 7.2)
- Alcoholic beverage consumption for at least three days during or after therapy. (4.3, 7.3)
- Severe renal impairment. (4.4)
- Women who are pregnant. (4.5, 8.1)
- Known hypersensitivity to product components. (4.6)

WARNINGS AND PRECAUTIONS

- Fetal Toxicity: Advise pregnant women of the risk throughout pregnancy for retardation of skeletal development seen in animal studies and permanent discoloration of teeth with tetracycline if used during the second or third trimester. (5.2, 8.1)
- Maternal Toxicity: Risk of hepatotoxicity in pregnant women with high doses of intravenous tetracycline also resulting in stillborn or premature birth. (5.3, 8.1)

- Tooth Enamel discoloration and hypoplasia: permanent discoloration may develop with use during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years). (5.4)
- Central and Peripheral Nervous System Effects: encephalopathy, convulsive seizures, aseptic meningitis and peripheral neuropathy with metronidazole, intracranial hypertension with tetracycline and neurotoxicity with bismuth-containing products. Monitor patients with CNS conditions closely and discontinue promptly if abnormal neurologic signs develop. (5.5)
- Photosensitivity: avoid exposure to sun and sun lamps. (5.7)
- Blood Dyscrasias: Use with caution in patients with a history of blood dyscrasias (5.9)
- Hepatic Impairment: Not recommended in patients with severe hepatic impairment. (5.10)
- Cutaneous Reactions: Stevens-Johnson, toxic epidermal necrolysis, DRESS syndrome. Discontinue treatment at the first evidence of a cutaneous reaction. (5.13)

ADVERSE REACTIONS

Most frequently reported adverse reactions ($\geq 5\%$); abnormal feces, diarrhea, nausea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact APTALIS Pharma US, Inc. at 1-800-472-2634 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Methoxyflurane: Risk of fatal renal toxicity; do not co-administer. (4.1, 7.1).
- Disulfiram: Psychotic reactions can occur; do not take concurrently or within the last 2 weeks of disulfiram. (4.2, 7.2)
- Alcohol: Abdominal cramps, nausea, vomiting, headaches, and flushing can occur; do not consume during therapy and for at least 3 days afterwards. (4.3, 7.3)
- Oral Contraceptives: Decreased efficacy possibly resulting in pregnancy; use a different or additional form of contraception. (5.14, 7.4)
- Anticoagulants: Potentiation of the anticoagulant effect; Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored. (5.14, 7.5)
- Lithium: Increased lithium serum concentrations; measure serum lithium and serum creatinine concentrations during therapy. (5.14, 7.6)
- Antacids, Multivitamins or Dairy Products: Decreased absorption of PYLERA; do not take concomitantly. (7.7)
- Busulfan: Increased busulfan serum concentrations; avoid concomitant use, monitor for busulfan toxicity (7.8)
- CYP inducers and CYP inhibitors: Prolonged or accelerated half-life of metronidazole or concomitant medications; use with caution (7.9, 7.10)

USE IN SPECIFIC POPULATIONS

- Lactation: A woman should pump and discard human milk for the duration of PYLERA therapy, and for 2 days after therapy ends, (8.2)
- Pediatric Use: Tetracycline may cause permanent discoloration of the teeth. Enamel hypoplasia has also been reported. Do not use in children less than 8 years of age. (5.4, 8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2017

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL FOR CARCINOGENICITY

Metronidazole has been shown to be carcinogenic in mice and rats. It is unknown whether metronidazole is associated with carcinogenicity in humans [see *Warning and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Eradication of *Helicobacter pylori* in Patients with Active Duodenal Ulcer or History of Duodenal Ulcer Disease

PYLERA in combination with omeprazole are indicated for the treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. The eradication of *Helicobacter pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

1.2 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of PYLERA and other antibacterial drugs, PYLERA should be used to treat only indicated infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

Administer three PYLERA capsules 4 times a day (after meals and at bedtime) for 10 days. One omeprazole 20 mg capsule should be taken twice a day with PYLERA after the morning and evening meal for 10 days (**Table 1**).

Table 1: Daily Dosing Schedule for PYLERA

| Time of dose | Number of capsules of PYLERA | Number of capsules of omeprazole 20 mg |
|--------------------|------------------------------|--|
| After morning meal | 3 | 1 |
| After lunch | 3 | 0 |
| After evening meal | 3 | 1 |
| At bedtime | 3 | 0 |

Instruct patients to swallow the PYLERA capsules whole with a full glass of water (8 ounces). Ingestion of adequate amounts of fluid, particularly with the bedtime dose, is recommended to reduce the risk of esophageal irritation and ulceration by tetracycline hydrochloride.

If a dose is missed, patients should continue the normal dosing schedule until medication is gone. Patients should not take double doses. If more than 4 doses are missed, the prescriber should be contacted.

3 DOSAGE FORMS AND STRENGTHS

Each PYLERA capsule contains 140 mg of bismuth subcitrate potassium, 125 mg of metronidazole, and a smaller capsule inside containing 125 mg of tetracycline hydrochloride. The capsules are white and opaque, with the APTALIS™ logo printed on the body and “BMT” printed on the cap.

4 CONTRAINDICATIONS

4.1 Methoxyflurane

Do not administer methoxyflurane to patients taking PYLERA. The concurrent use of tetracycline hydrochloride, a component of PYLERA, with methoxyflurane has been reported to result in fatal renal toxicity [see [Drug Interactions \(7.1\)](#)].

4.2 Disulfiram

PYLERA is contraindicated in patients who have taken disulfiram within the last two weeks. Psychotic reactions have been reported in alcoholic patients who are using metronidazole, a component of PYLERA, and disulfiram concurrently [see [Drug Interactions \(7.2\)](#)].

4.3 Alcohol

Alcoholic beverages or other products containing propylene glycol should not be consumed during and for at least 3 days after therapy with PYLERA. A disulfiram-like reaction (abdominal cramps, nausea, vomiting, headaches, and flushing) may occur due to the interaction between alcohol or propylene glycol and metronidazole, a component of PYLERA [see [Drug Interactions \(7.3\)](#)].

4.4 Severe Renal Impairment

PYLERA is contraindicated in patients with severe renal impairment. The antianabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN) [see [Adverse Reactions \(6.3\)](#)]. In patients with significantly impaired renal function, higher serum concentrations of tetracyclines may lead to azotemia, hyperphosphatemia, and acidosis.

4.5 Pregnancy

PYLERA is contraindicated during pregnancy [see [Use in Specific Populations \(8.1\)](#)].

4.6 Hypersensitivity Reactions

PYLERA is contraindicated in patients with known hypersensitivity (e.g. urticaria, erythematous rash, flushing, and fever) to bismuth subcitrate potassium, metronidazole or other nitroimidazole derivatives, or tetracycline [see [Adverse Reactions \(6.3\)](#)].

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Carcinogenicity

Metronidazole, a component of PYLERA, has been shown to be carcinogenic in mice and rats. Tumors affecting the liver, lungs, mammary and lymphatic tissues have been detected in several studies of metronidazole in rats and mice, but not hamsters [see [Nonclinical Toxicology \(13\)](#)]. It is unknown whether metronidazole is associated with carcinogenicity in humans.

5.2 Fetal Toxicity

Tetracycline can cause fetal harm when administered to a pregnant woman. Based on animal data, use of drugs of the tetracycline class during the second and third trimester of pregnancy can cause permanent discoloration of the teeth (yellow-gray brown) and possibly inhibit bone development [see [Warnings and Precautions \(5.4\)](#)]. Administration of oral tetracycline to pregnant rats at various doses resulted in yellow fluorescence in teeth and bones in the newborn animals. If PYLERA is used during pregnancy, or if the patient becomes pregnant while taking PYLERA, advise the patient of the potential risk to the fetus [see [Contraindications \(4.5\)](#) and [Use in Specific Populations \(8.1\)](#)].

5.3 Maternal Toxicity

Tetracycline, a component of PYLERA, administered during pregnancy at high doses (> 2 g IV) was associated with rare but serious cases of maternal hepatotoxicity. This syndrome may result in stillborn or premature birth due to maternal pathology [see [Contraindications \(4.5\)](#) and [Use in Specific Populations \(8.1\)](#)].

5.4 Tooth Enamel Discoloration and Hypoplasia

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 drug, but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. PYLERA, therefore, should not be used in this age group unless other drugs are not likely to be effective or are contraindicated [see [Use in Specific Populations \(8.4\)](#)].

5.5 Central and Peripheral Nervous System Effects

Metronidazole: Convulsive seizures, encephalopathy, aseptic meningitis and peripheral neuropathy (including optic neuropathy) have been reported. Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, and dysarthria. CNS lesions seen on MRI have been described in reports of encephalopathy. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible. Peripheral neuropathy, mainly of sensory type has been reported and is characterized by numbness or paresthesia of an extremity. Aseptic meningitis symptoms may occur within hours of dose administration and generally resolve after metronidazole therapy is discontinued.

Tetracycline: Intracranial hypertension (IH), including pseudotumor cerebri, has been associated with the use of tetracyclines. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Concomitant use of isotretinoin should be avoided because isotretinoin is also known to cause IH.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.

Bismuth-containing products: Cases of neurotoxicity associated with excessive doses of various bismuth-containing products have been reported. Effects have been reversible with discontinuation of bismuth therapy.

The appearance of abnormal neurologic signs and symptoms demands the prompt evaluation of the benefit/risk ratio of the continuation of PYLERA therapy [see [Adverse Reactions \(6.3\)](#)].

5.6 Development of Potential for Microbial Overgrowth

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with an antifungal agent. As with other antibacterial drugs, use of tetracycline hydrochloride may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, discontinue PYLERA and institute appropriate therapy.

5.7 Photosensitivity

Photosensitivity, manifested by an exaggerated sunburn reaction, has been observed in patients taking tetracycline [see [Adverse Reactions \(6.3\)](#)]. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs. Instruct patients taking PYLERA to avoid exposure to the sun or sun lamps. Discontinue treatment at the first evidence of skin erythema.

5.8 Darkening of the Tongue and/or Black Stool

Bismuth subcitrate potassium may cause temporary and harmless darkening of the tongue and/or black stools, generally reversible within several days after treatment is stopped [see [Adverse Reactions \(6.1\)](#)]. Stool darkening should not be confused with melena.

5.9 Use in Patients with Blood Dyscrasias

Metronidazole is a nitroimidazole, and should be used with care in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy [see [Adverse Reactions \(6.3\)](#)].

5.10 Increased Plasma Concentrations in Patients with Hepatic Impairment

Patients with hepatic impairment metabolize metronidazole slowly, with resultant accumulation of metronidazole in the plasma. Patients with mild to moderate hepatic impairment should be monitored for metronidazole associated adverse events. PYLERA is not recommended in patients with severe hepatic impairment (Child-Pugh C) [see [Clinical Pharmacology \(12.3\)](#)].

5.11 Laboratory Test Interactions

Bismuth absorbs x-rays and may interfere with x-ray diagnostic procedures of the gastrointestinal tract.

Bismuth subcitrate potassium may cause a temporary and harmless darkening of the stool. However, this change 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 ($\text{NAD}^+ \rightleftharpoons \text{NADH}$). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

5.12 Development of Drug Resistant Bacteria

Prescribing PYLERA in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.13 Cutaneous Reactions

Skin and subcutaneous disorders including Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS syndrome (drug rash with eosinophilia and systemic symptoms) have been reported. Discontinue treatment at the first evidence of a cutaneous reaction [see [Adverse Reactions \(6.2\)](#)].

5.14 Drug Interactions

Oral Contraceptives

Concurrent use of PYLERA with oral contraceptive may make oral contraceptives less effective due to an interaction with the tetracycline component of PYLERA. Breakthrough bleeding has been reported. Advise women of child-bearing potential to use a different or additional form of contraception while taking PYLERA [see [Drug Interactions \(7.4\)](#)].

Anticoagulants

PYLERA may alter the anticoagulant effects of warfarin and other oral coumarin anticoagulants. Metronidazole has been reported to potentiate the anticoagulant effect of warfarin, and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. Tetracycline has been shown to depress plasma prothrombin activity. Closely monitor prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests if PYLERA is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding [see *Drug Interactions (7.5)*].

Lithium

In patients stabilized on relatively high doses of lithium, short-term use of PYLERA may cause elevation of serum lithium concentrations and signs of lithium toxicity due to the interaction between metronidazole and lithium. Monitor serum lithium and serum creatinine concentrations daily for several days after beginning treatment with PYLERA to detect any increase that may precede clinical symptoms of lithium toxicity [see *Drug Interactions (7.6)*].

Busulfan

Metronidazole has been reported to increase plasma concentrations of busulfan, which can result in an increased risk for serious busulfan toxicity. Do not administer PYLERA concomitantly with busulfan unless the benefit outweighs the risk. If no therapeutic alternatives to PYLERA are available, and concomitant administration with busulfan is medically needed, Monitor for busulfan toxicity and busulfan plasma concentrations and adjust the busulfan dose accordingly [see *Drug Interactions (7.8)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of PYLERA plus omeprazole (OBMT) to eradicate *Helicobacter pylori* was assessed in an open-label, randomized, active-controlled clinical trial conducted in North America. The duration of treatment was 10 days with 147 patients exposed to PYLERA plus omeprazole (OBMT) and 152 exposed to control, consisting of omeprazole, amoxicillin, and clarithromycin (OAC). The age of the population in the study ranged from 18 to 75 years, with 59% male patients and 59% Caucasian patients.

Adverse drug reactions were reported in 58% of patients in the OBMT group and 59% of patients in the OAC group. There were no adverse reactions leading to discontinuation of the study during the clinical trial.

Adverse reactions with an incidence of $\geq 5\%$ in OBMT group include abnormal feces, diarrhea, nausea, and headache. Adverse drug reactions with an incidence of $\geq 5\%$ in OAC group include diarrhea, dysgeusia, dyspepsia, nausea and headache.

Table 2 lists adverse reactions with an incidence of $\geq 1\%$, in either groups (OBMT vs OAC) and in order of decreasing incidence for the OBMT group.

Table 2: Adverse reactions with an incidence of $\geq 1\%$ from North American trial, [n (%)]

| Preferred Term | OBMT* (n = 147) | OAC** (n = 152) |
|--|-----------------|-----------------|
| <u>Gastrointestinal disorders</u> | | |
| Abnormal feces*** | 23 (15.6%) | 7 (4.6%) |
| Nausea | 12 (8.2%) | 14 (9.2%) |
| Diarrhea | 10 (6.8%) | 20 (13.2%) |
| Abdominal Pain | 7 (4.8%) | 2 (1.3%) |
| Dyspepsia | 4 (2.7%) | 10 (6.6%) |
| Constipation | 2 (1.4%) | 5 (3.3%) |
| Dry Mouth | 2 (1.4%) | 1 (0.7%) |
| Flatulence | 0 | 4 (2.6%) |
| Glositis | 0 | 2 (1.3%) |
| <u>General disorders and administration site conditions</u> | | |
| Asthenia | 5 (3.4%) | 2 (1.3%) |
| <u>Infections and infestations</u> | | |
| Vaginal infection | 4 (2.7%) | 3 (2.0%) |
| <u>Nervous system disorders</u> | | |
| Headache | 8 (5.4%) | 8 (5.3%) |
| Dysgeusia | 6 (4.1%) | 18 (11.8%) |
| Dizziness | 4 (2.7%) | 4 (2.6%) |

| Investigations | | |
|---|----------|----------|
| Laboratory test abnormal | 3 (2.0%) | 4 (2.6%) |
| Alanine aminotransferase increased | 2 (1.4%) | 0 |
| Aspartate aminotransferase increased | 2 (1.4%) | 0 |
| Renal and urinary disorders | | |
| Urine abnormality | 2 (1.4%) | 0 |
| Skin and subcutaneous tissue disorders | | |
| Rash Maculo-Papular | 2 (1.4%) | 0 |
| Rash | 1 (0.7%) | 3 (2.0%) |
| Pruritus | 0 | 4 (2.6%) |

*OBMT = Omeprazole + PYLERA

**OAC = Omeprazole + Amoxicillin + Clarithromycin;

*** Dark stools [see [Warnings and Precautions \(5.8\)](#)]

Adverse reactions with an incidence of <1% for OBMT group are: back pain, vomiting, tongue darkening [see [Warnings and Precautions \(5.8\)](#)], anxiety, gastritis, gastroenteritis, myalgia, chest pain, increased appetite, blood creatine phosphokinase increased, malaise, somnolence, tachycardia, duodenal ulcer, visual disturbance, weight increased.

6.2 Postmarketing Experience

Additionally, the following adverse reactions, presented by system organ class in alphabetical order, have been identified during post approval use of PYLERA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Gastrointestinal disorders*: abdominal distention, eructation, flatulence
- *General disorders and administration site conditions*: chest discomfort, fatigue.
- *Infections and infestations*: candidiasis, pseudomembranous colitis (*Clostridium difficile* colitis).
- *Nervous Systems*: peripheral neuropathy.
- *Skin and subcutaneous disorders*: Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS syndrome (drug rash with eosinophilia and systemic symptoms)

6.3 Other Important Adverse Reactions from Labeling for the Individual Components of PYLERA

Metronidazole

Blood and Lymphatic system disorders: Reversible neutropenia (leucopenia) in cases of prolonged treatment; rarely reversible thrombocytopenia however no persistent hematological abnormalities attributable to metronidazole have been observed [see [Warnings and Precautions \(5.9\)](#)].

Cardiac disorders: Flattening of the T-wave.

Gastrointestinal disorders: Nausea, vomiting, diarrhea, abdominal pain, constipation, anorexia, metallic taste, furry tongue, glossitis, stomatitis and candida overgrowth.

Hypersensitivity/Immune system disorders: Urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever [see [Contraindications \(4.5\)](#)].

Metabolism and nutrition disorders: Pancreatitis.

Nervous system disorders: Convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, headache, syncope, dizziness, vertigo, incoordination, ataxia, confusion, dysarthria, irritability, depression, weakness, and insomnia [see [Warnings and Precautions \(5.5\)](#)].

Dermatologic disorders: Erythematous rash and pruritus.

Renal and urinary disorders: Dysuria, cystitis, polyuria, incontinence, darkened urine, and a sense of pelvic pressure.

Other: Dyspareunia, decrease of libido, proctitis, joint pains.

Tetracycline Hydrochloride

Blood and lymphatic system disorders: Hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, neutropenia, and eosinophilia.

Gastrointestinal disorders: Nausea, vomiting, diarrhea, anorexia, glossitis, black hairy tongue, dysphagia, enterocolitis, inflammatory lesions (with *Candida* overgrowth) in the anogenital region, esophagitis and esophageal ulceration.

Nervous system disorders: Intracranial hypertension including pseudotumor cerebri, tinnitus, and myasthenic syndrome.

Renal and urinary disorders: Increased BUN.

Skin and subcutaneous tissue disorders: Maculopapular and erythematous rashes, onycholysis, discoloration of the nails, exfoliative dermatitis and photosensitivity have been rarely reported [see [Warnings and Precautions \(5.13\)](#)].

Liver: Hepatotoxicity and liver failure.

Hypersensitivity reactions: Urticaria, angioedema, anaphylaxis, Henoch-Schonlein purpura, pericarditis, exacerbation of systemic lupus erythematosus, and serum sickness-like reactions.

7 DRUG INTERACTIONS

7.1 Methoxyflurane

Do not administer methoxyflurane to patients taking PYLERA. The concurrent use of tetracycline hydrochloride, a component of PYLERA, with methoxyflurane has been reported to result in fatal renal toxicity [see [Contraindications \(4.1\)](#)].

7.2 Disulfiram

Psychotic reactions have been reported in alcoholic patients who are using metronidazole, a component of PYLERA and disulfiram concurrently. PYLERA should not be given to patients who have taken disulfiram within the last two weeks [see [Contraindications \(4.2\)](#)].

7.3 Alcohol

Consumption of alcoholic beverages or administration of other products containing propylene glycol during treatment with PYLERA and for at least 3 days afterwards may cause a disulfiram-like reaction (abdominal cramps, nausea, vomiting, headaches, and flushing) due to the interaction between alcohol or propylene glycol and metronidazole, a component of PYLERA. Discontinue alcoholic beverage or other products containing propylene glycol during and for at least 3 days after therapy with PYLERA [see [Contraindications \(4.3\)](#)].

7.4 Oral Contraceptives

Concurrent use of PYLERA with oral contraceptive may make oral contraceptives less effective due to an interaction with the tetracycline component of PYLERA. Breakthrough bleeding has been reported. Women of child-bearing potential should use a different or additional form of contraception while taking PYLERA [see [Warnings and Precautions \(5.14\)](#)].

7.5 Anticoagulants

PYLERA may alter the anticoagulant effects of warfarin and other oral coumarin anticoagulants. Metronidazole has been reported to potentiate the anticoagulant effect of warfarin, and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. Tetracycline has been shown to depress plasma prothrombin activity. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if PYLERA is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding [see [Warnings and Precautions \(5.14\)](#)].

7.6 Lithium

In patients stabilized on relatively high doses of lithium, short-term use of PYLERA may cause elevation of serum lithium concentrations and signs of lithium toxicity due to the interaction between metronidazole and lithium. Serum lithium and serum creatinine concentrations should be monitored several days after beginning treatment with PYLERA to detect any increase that may precede clinical symptoms of lithium toxicity [see [Warnings and Precautions \(5.14\)](#)].

7.7 Antacids, Multivitamins, or Dairy Products

The absorption of PYLERA may be reduced if administered with antacids containing aluminium, calcium, or magnesium; preparations containing iron, zinc, or sodium bicarbonate; or milk or dairy products due to the interaction between these products and tetracycline. These products should not be consumed concomitantly with PYLERA. However, the clinical significance of reduced tetracycline systemic exposure is unknown as the relative contribution of systemic versus local antimicrobial activity against *Helicobacter pylori* has not been established.

7.8 Busulfan

Metronidazole has been reported to increase plasma concentrations of busulfan, which can result in an increased risk for serious busulfan toxicity. Do not administer PYLERA concomitantly with busulfan unless the benefit outweighs the risk. If no therapeutic

alternatives to PYLERA are available, and concomitant administration with busulfan is medically needed, monitor for busulfan toxicity and busulfan plasma concentrations and adjust the busulfan dose accordingly [see [Warnings and Precautions \(5.14\)](#)].

7.9 Inhibitors of CYP450 liver enzymes

The simultaneous administration of PYLERA and drugs that inhibit microsomal liver enzymes, such as cimetidine, may result in a prolonged half-life and decreased plasma clearance of metronidazole.

7.10 Inducers of CYP450 liver enzymes

The simultaneous administration of PYLERA and drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma concentrations of metronidazole. Impaired clearance of phenytoin has also been reported in this situation. Monitor phenytoin concentrations during treatment with PYLERA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

PYLERA is contraindicated in women who are pregnant because treatment of *Helicobacter pylori* infection can be delayed in pregnant women, and the use of drugs of the tetracycline class during the second and third trimester pregnancy can also cause permanent discoloration of the teeth (yellow-gray brown) and possibly inhibit bone development [See [Warnings and Precautions \(5.2\) and Data](#)]. Administration of oral tetracycline to pregnant rats at various doses resulted in yellow fluorescence in teeth and bones in the newborn animals. There are maternal risks with high intravenous doses of tetracycline [see [Clinical Considerations](#)]. Metronidazole usage in pregnancy has been associated with certain congenital anomalies [see [Data](#)]. In animals, no fetotoxicity was observed when metronidazole was orally administered to pregnant mice at approximately 5% of the indicated human dose. There are no human or animal data on the use of bismuth subcitrate potassium during pregnancy. Although there are data on the separate components, there are no available data on the use of PYLERA in pregnant women.

Clinical Considerations

Maternal Adverse Reactions

Tetracycline administered during pregnancy at high doses (> 2 g IV) was associated with rare but serious cases of maternal hepatotoxicity. This syndrome may result in stillborn or premature birth due to maternal pathology [see [Warnings and Precautions \(5.3\)](#)].

Data

Human Data

Tetracycline

Published case reports have described the yellowing of bones and teeth in human infants exposed to tetracycline during the second and third trimester of pregnancy. The yellowing is caused by the direct deposition of tetracycline during the mineralization process. This discoloration is more common during long-term use of the drug but has also been observed following repeated short-term courses. All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in fibula growth rate was observed in premature infants given oral tetracycline in doses of 25 mg/kg every six hours. The effect resolved when the drug was discontinued. One long-term follow-up study in children exposed to tetracycline in-utero showed no adverse effects on bone growth and development.

Metronidazole

There are published data from case-control studies, cohort studies, and 2 meta-analyses that include more than 5000 pregnant women who used metronidazole during pregnancy. Many studies included first trimester exposures. One study showed an increased risk of cleft lip, with or without cleft palate, in infants exposed to metronidazole in-utero; however, these findings were not confirmed. In addition, more than ten randomized, placebo-controlled clinical trials enrolled more than 5000 pregnant women to assess the use of antibiotic treatment (including metronidazole) for bacterial vaginosis on the incidence of preterm delivery. Most studies did not show an increased risk for congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy. Three studies conducted to assess the risk of infant cancer following metronidazole exposure during pregnancy did not show an increased risk; however, the ability of these studies to detect such a signal was limited.

Bismuth subcitrate potassium

There are no human data on the use of bismuth subcitrate potassium during pregnancy.

Animal Data

Tetracycline

Results of animal studies indicate that tetracycline crosses the placenta, is found in fetal tissues, and can have toxic effects on the developing fetus (often related to reversible retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. Multiple studies of limited design were conducted with pregnant and lactating female rats that resulted in fetuses and neonates with yellow discoloration of bones and teeth.

Metronidazole

Metronidazole crosses the placental barrier. No fetotoxicity was observed when metronidazole was administered orally to pregnant mice at 10 mg/kg/day, approximately 5 percent of the indicated human dose (1500 mg/day) based on body surface area; 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.

Bismuth subcitrate potassium

Animal reproductive studies have not been conducted with bismuth subcitrate potassium.

8.2 Lactation

Risk Summary

Two of the individual components of PYLERA, tetracycline and metronidazole, are present in human milk at concentrations similar to maternal serum levels. It is not known whether bismuth subcitrate, the third component of PYLERA is present in human milk. It is not known what effect metronidazole, tetracycline or bismuth has on the breastfed infant or on milk production. Tetracycline binds with calcium in human milk [see [Clinical Pharmacology \(12.3\)](#)]. Data indicate that oral absorption of tetracycline in infants is low due to the calcium binding in human milk. Metronidazole transfers to human milk, and infant serum levels can be close to or comparable to infant therapeutic levels. Because of the potential risk of tumorigenicity shown in animal studies with metronidazole, a woman should pump and discard human milk for the duration of PYLERA therapy, and for 2 days after therapy ends, and feed her infant stored human milk (collected prior to therapy) or formula.

8.4 Pediatric Use

Safety and effectiveness of PYLERA in pediatric patients infected with *Helicobacter pylori* have not been established.

Tetracycline use in children may cause permanent discoloration of the teeth. Enamel hypoplasia has also been reported. PYLERA should not be used in children up to 8 years of age [see [Warnings and Precaution \(5.4\)](#)].

8.5 Geriatric Use

Clinical studies of PYLERA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, elderly patients may have a greater frequency of decreased hepatic, renal, or cardiac function, and concomitant diseases or other drug therapies. Bismuth subcitrate potassium, a component of PYLERA, is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, additional monitoring may be required [see [Contraindications \(4.4\)](#)].

8.6 Renal Impairment

The antianabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with severe renal impairment, higher serum concentrations of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis [see [Contraindications \(4.4\)](#)].

8.7 Hepatic Impairment

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in plasma. Patients with mild to moderate hepatic impairment should be monitored for metronidazole associated adverse events. PYLERA is not recommended in patients with severe hepatic impairment [see [Warnings and Precautions \(5.10\)](#), [Clinical Pharmacology \(12.3\)](#)].

10 OVERDOSAGE

In case of an overdose, patients should contact a physician, poison control center, or emergency room. The available overdose information for each of the individual components in PYLERA (Metronidazole, Tetracycline and Bismuth subcitrate potassium) are summarized below:

Metronidazole:

Single oral doses of metronidazole, up to 15 g, have been reported in suicide attempts and accidental overdoses. Symptoms reported include nausea, vomiting, and ataxia. Metronidazole is dialyzable.

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 of Overdosage

There is no specific antidote for metronidazole overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

Tetracycline:

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

Bismuth subcitrate potassium:

Symptoms of a bismuth subcitrate potassium overdosage are not known.

11 DESCRIPTION

PYLERA capsules are a combination antimicrobial product containing bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride for oral administration. Each size 0 elongated capsule contains:

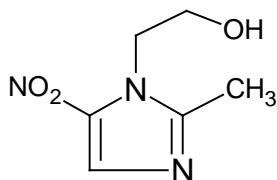
- bismuth subcitrate potassium, 140 mg
- metronidazole, 125 mg
- smaller capsule (size 3) containing tetracycline hydrochloride, 125 mg

Tetracycline hydrochloride is encapsulated within a smaller capsule to create a barrier to avoid contact with bismuth subcitrate potassium.

Each PYLERA capsule contains the following inactive ingredients: Magnesium Stearate NF, Lactose Monohydrate NF, Talc USP, Gelatin USP, and Titanium Dioxide NF, Printed in red ink.

Bismuth subcitrate potassium is a white or almost white powder. It is a soluble, complex bismuth salt of citric acid. The schematized empirical molecular formula of bismuth subcitrate potassium is $\text{Bi}(\text{Citrate})_2\text{K}_5 \cdot 3 \text{H}_2\text{O}$. The equivalent theoretical molecular formula is $\text{BiC}_{12}\text{H}_{14}\text{K}_5\text{O}_{17}$. The molecular mass of the theoretical molecular formula of a single unit of bismuth subcitrate potassium is 834.71.

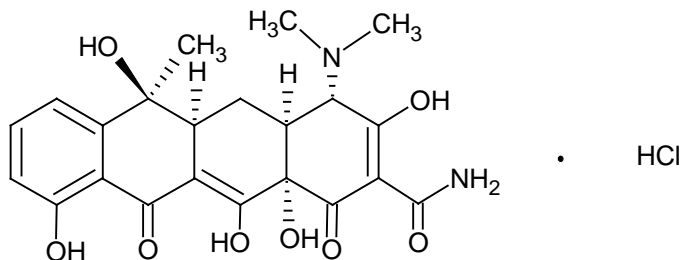
Metronidazole is a white to pale yellow crystalline powder. Metronidazole is 2-methyl-5-nitroimidazole-1-ethanol, with a molecular



formula of $\text{C}_6\text{H}_9\text{N}_3\text{O}_3$ and the following structural formula:

Molecular weight: 171.2

Tetracycline hydrochloride is a yellow, odorless, crystalline powder. Tetracycline hydrochloride is stable in air, but exposure to strong sunlight causes it to darken. Tetracycline hydrochloride is (4S,4aS,5aS,6S,12aS)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-penta-hydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide hydrochloride, with a molecular formula of $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_8 \cdot \text{HCl}$ and the following structural formula:



Molecular weight: 480.90

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PYLERA is a combination of antibacterial agents (metronidazole and tetracycline hydrochloride) and bismuth subcitrate potassium [see [Microbiology \(12.4\)](#)].

12.3 Pharmacokinetics

The pharmacokinetics of the individual components of PYLERA, bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride are summarized below. In addition, two studies on PYLERA were conducted to determine the effect of co-administration on the pharmacokinetics of the components.

Bismuth Subcitrate Potassium (Bismuth)

Absorption and Distribution

Orally absorbed bismuth is distributed throughout the entire body. Bismuth is highly bound to plasma proteins (>90%).

Metabolism and Excretion

The elimination half-life of bismuth is approximately 5 days in both blood and urine. Elimination of bismuth is primarily through urinary and biliary routes. The rate of renal elimination appears to reach steady state 2 weeks after treatment discontinuation with similar rates of elimination at 6 weeks after discontinuation. The average urinary elimination of bismuth is 2.6% per day in the first two weeks after discontinuation (urine drug concentrations 24 to 250 mcg/mL) suggesting tissue accumulation and slow elimination.

Metronidazole

Absorption and Distribution

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 500 mg producing a peak plasma concentration of 12 mcg/mL.

Metronidazole appears in the plasma mainly as unchanged compound with lesser quantities of the 2-hydroxymethyl metabolite also present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Metronidazole also appears in cerebrospinal fluid, saliva, and breast milk in concentration similar to those found in plasma.

Metabolism and Excretion

The average elimination half-life of metronidazole 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/1.73m².

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

Absorption, Distribution, Metabolism and Excretion

Tetracycline hydrochloride is absorbed (60%-90%) in the stomach and upper small intestine. The presence of food, milk or cations may significantly decrease the extent of absorption. In the plasma, tetracycline is bound to plasma proteins in varying degrees. It is concentrated by the liver in the bile and excreted in the urine and feces at high concentrations in biologically active form.

Tetracycline hydrochloride is distributed into most body tissues and fluids. It is distributed into the bile and undergoes varying degrees of enterohepatic recirculation. Tetracycline hydrochloride tends to localize in tumors, necrotic or ischemic tissue, liver and spleen and form tetracycline-calcium orthophosphate complexes at sites of new bone formation or tooth development. Tetracycline readily crosses the placenta and is excreted in high amounts in breast milk.

PYLERA Capsules

A comparative bioavailability study of metronidazole (375 mg), tetracycline hydrochloride (375 mg) and bismuth subcitrate potassium (420 mg, equivalent to 120 mg Bi₂O₃) administered as PYLERA or as 3 separate capsule formulations administered simultaneously was conducted in healthy male volunteers. The pharmacokinetic parameters for the individual drugs, when administered as separate capsule formulations or as PYLERA, are similar as shown in **Table 3**.

Table 3: Mean (%CV) Pharmacokinetic Parameters for Metronidazole, Tetracycline hydrochloride, and Bismuth Subcitrate Potassium in Healthy Volunteers (N=18)

| | | C_{max} (ng/mL) (%C.V.**) | AUC_T (ng · h/mL) (%C.V.**) | AUC_∞ (ng · h/mL) (%C.V.**) |
|----------------------|-----------------------|--|--|--|
| Metronidazole | Metronidazole Capsule | 9044 (20) | 80289 (15) | 81849 (16) |
| | PYLERA* | 8666.3 (22) | 83018 (17) | 84413 (17) |
| Tetracycline | Tetracycline Capsules | 748.0 (40) | 9544 (55) | 9864 (53) |
| | PYLERA* | 774 (47) | 9674 (50) | 9987 (49) |
| Bismuth | Bismuth Capsule | 22 (123) | 47 (129) | 65.4 (113) |
| | PYLERA* | 17 (202) | 43 (191) | 57 (178) |

*PYLERA given as a single dose of 3 capsules

**C.V. – Coefficient Variation

Effect of Bismuth on the Bioavailability of Tetracycline Hydrochloride

There is an anticipated reduction in tetracycline hydrochloride systemic absorption due to an interaction with bismuth. The effect of a reduced tetracycline hydrochloride systemic exposure, due to an interaction with bismuth, on the clinical efficacy of PYLERA is not thought to be clinically meaningful as the contribution of systemic, as compared to local, antimicrobial activity against *Helicobacter pylori* has not been established.

Effect of Food on the Bioavailability of PYLERA

The pharmacokinetic parameters for metronidazole, tetracycline hydrochloride and bismuth were also determined when PYLERA was administered under fasting and fed conditions, as shown in **Table 4**. Food reduced the systemic absorption of all three PYLERA components, with AUC values for metronidazole, tetracycline hydrochloride and bismuth being reduced by 6%, 34% and 60%, respectively. Reduction in the absorption of all three PYLERA components in the presence of food is not considered to be clinically significant. PYLERA should be given after meals and at bedtime, in combination with omeprazole twice a day.

Table 4: Mean PYLERA Pharmacokinetic Parameters in Fasted and Fed States (N=18)*

| | FED | | | FASTED | | |
|--|--------------------|--------------------|--------------------|---------------------|--------------------|--------------------|
| | metronidazole | tetracycline | bismuth | metronidazole | tetracycline | bismuth |
| C_{max} (ng/mL) (%C.V.) | 6835.0 (13) | 515.8 (36) | 1.7 (61) | 8666.3 (22) | 773.8 (47) | 16.7 (202) |
| T_{max} (hours)** (range) | 3.0 (1.3 – 4.0) | 4.0 (2.5 – 5.0) | 3.5 (0.8 – 6.0) | 0.75 (0.5 – 3.5) | 3.3 (1.3 – 5.0) | 0.6 (0.5 – 1.7) |
| AUC_∞ (ng · h/mL) (%C.V.) | 79225.6 (18) | 5840.1 (312) | 18.4 (116) | 84413.6 (17) | 9986.7 (49) | 56.5 (178) |

*PYLERA given as a single dose of 3 capsules

**T_{max} is expressed as median (range)

Effect of Omeprazole on the Bioavailability of Bismuth

The effect of omeprazole on bismuth absorption was assessed in 34 healthy volunteers given PYLERA (four times daily) with or without omeprazole (20 mg twice daily) for 6 days. In the presence of omeprazole, the extent of absorption of bismuth from PYLERA was significantly increased, compared to when no omeprazole was given (**Table 5**). Concentration-dependent neurotoxicity is associated with long-term use of bismuth and not likely to occur with short-term administration or at steady state concentrations below 50 ng/mL. One subject transiently achieved a maximum bismuth concentration (C_{max}) higher than 50 ng/mL (73 ng/mL) following multiple dosing of PYLERA with omeprazole. The patient did not exhibit symptoms of neurotoxicity during the study. There is no clinical evidence to suggest that short-term exposure to bismuth C_{max} concentrations above 50 ng/mL is associated with neurotoxicity.

Table 5: Mean Bismuth Pharmacokinetic Parameters following PYLERA Administration* With and Without Omeprazole (N=34)

| Parameter | Without omeprazole | | With omeprazole | |
|------------------------------------|--------------------|---------|-----------------|---------|
| | Mean | %C.V.** | Mean | %C.V.** |
| C_{max} (ng/mL) | 8.1 | 84 | 25.5 | 69 |
| AUC_T (ng · h/mL) | 48.5 | 28 | 140.9 | 42 |

*PYLERA given as 3 capsules four times daily for 6 days with or without 20 mg omeprazole twice daily

**C.V. – Coefficient Variation

12.4 Microbiology

Mechanism of Action

PYLERA is a combination of antibacterial agents (metronidazole and tetracycline hydrochloride) and bismuth subcitrate potassium. Tetracycline hydrochloride interacts with the 30S subunit of the bacterial ribosome and inhibits protein synthesis. Metronidazole's antibacterial mechanism of action in an anaerobic environment is not fully understood but a possible mechanism includes reduction by intracellular electron transport proteins after entry into the organism. Because of this alteration to the metronidazole molecule, a concentration gradient is created and maintained which promotes the drug's intracellular transport. Presumably, free radicals are formed which, in turn, react with cellular components resulting in death of bacteria. The antibacterial action of bismuth salts is not well understood.

Antimicrobial Activity

PYLERA plus omeprazole therapy has been shown to be active against most isolates of *Helicobacter pylori* both *in vitro* and in clinical infections [see [Clinical Studies \(14\)](#)].

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide results of *in vitro* susceptibility test results for antimicrobial drug products used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial or community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The agar dilution procedure using Mueller-Hinton agar (MHA) supplemented with 5% v/v aged (≥ 2 -week old) sheep blood is recommended for testing *H. pylori* [See [References \(15\)](#)]. No interpretive criteria have been established for testing metronidazole or tetracycline against *H. pylori*.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test [See [References \(15\)](#)]. Standard metronidazole or tetracycline powder should provide the following range of MIC values noted in Table 6.

Table 6. Acceptable Quality Control Ranges for Metronidazole and Tetracycline

| QC Strain | Agar Dilution (mcg/mL) |
|---------------------------------------|---------------------------|
| <i>Helicobacter pylori</i> ATCC 43504 | |
| Metronidazole | 64 – 256 |
| Tetracycline | 0.12 – 1 |

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed to evaluate the effect of PYLERA on carcinogenesis, mutagenesis, or impairment of fertility.

Bismuth Subcitrate Potassium

No carcinogenicity or reproductive toxicity studies have been conducted with bismuth subcitrate potassium. Bismuth subsalicylate did not show mutagenic potential in the NTP *Salmonella* plate assay.

Metronidazole

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 the highest dose levels, (approximately 500 mg/kg/day, which is approximately 1.6 times the indicated human dose for a 60 kg adult based on body surface area) 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. 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.

Fertility studies have been conducted with male rats and mice with divergent results. Metronidazole, at doses up to 400 mg/kg/day (approximately 3 times the indicated human dose based on mg/m²) for 28 days, failed to produce any adverse effects on fertility and testicular function in male rats. Rats treated with up to 400 mg/kg/day for 6 weeks or longer, showed severe degeneration of the seminiferous epithelium in the testes which was associated with a marked decrease in testicular spermatid counts and epididymal sperm counts and a marked decrease in fecundity. These effects were partially reversible.

Fertility studies have been performed in male mice at doses up to six times the maximum recommended human dose based upon mg/m² and have revealed no evidence of impaired fertility. Another fertility study was performed in male mice at oral doses of 500 mg/kg/day (approximately 2 times the indicated human dose based on mg/m²) for 14 days. Metronidazole significantly decreased testes and epididymides weight, decreased sperm viability, and increased the incidence of abnormal sperm. The viability of sperm was normal by 2 months after the start of the treatment.

Tumors affecting the liver, lungs, mammary, and lymphatic tissues have been detected in several studies of metronidazole in rats and mice, but not hamsters.

Pulmonary tumors have been observed in all six reported studies in the mouse, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). Malignant liver tumors were increased in male mice treated at approximately 1500 mg/m² (similar to the maximum recommended daily dose, based on body surface area comparisons). Malignant lymphomas and pulmonary neoplasms were also increased with lifetime feeding of the drug to mice. Mammary and hepatic tumors were increased among female rats administered oral metronidazole compared to concurrent controls. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has shown mutagenic activity in *in vitro* assay systems including the Ames test. Studies in mammals *in vivo* have failed to demonstrate a potential for genetic damage.

Tetracycline hydrochloride

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.

There was evidence of mutagenicity by tetracycline hydrochloride in two *in vitro* mammalian cell assay systems (L51784y mouse lymphoma and Chinese hamster lung cells).

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.

14 CLINICAL STUDIES

14.1 Eradication of *Helicobacter pylori* in Patients with Active Duodenal Ulcer or History of Duodenal Ulcer Disease

An open-label, parallel group, active-controlled, multicenter study in *Helicobacter pylori* positive patients with current duodenal ulcer or a history of duodenal ulcer disease was conducted in the United States and Canada (the North American Study).

Patients were randomized to one of the following 10-day treatment regimens:

- Three (3) PYLERA capsules four times daily, after meals and at bedtime plus 20 mg omeprazole twice a day after the morning and evening meals (OBMT).
- Clarithromycin 500 mg plus 1000 mg amoxicillin plus 20 mg omeprazole twice a day before the morning and evening meals (OAC).

H. pylori eradication rates, defined as two negative ¹³C-urea breath tests performed at 4 and 8 weeks post-therapy are shown in **Table 7** for OBMT and OAC. The eradication rates for both groups were found to be similar using either the Per Protocol (PP) or Modified Intent-to-Treat (MITT) populations.

Table 7. *Helicobacter pylori* Eradication at 8 Weeks after 10 Day Treatment Regimen Percent (%) of Patients Cured [95% Confidence Interval] (Number of Patients)

| | Treatment Group | | Difference |
|--|-----------------|---------------------|------------|
| | OBMT* | OAC* * ^c | |
| | | | |

| | | | |
|---------------------------------------|----------------------------------|----------------------------------|----------------------|
| Per Protocol ^a | 92.5% [87.8, 97.2] (n=120) | 85.7% [76.9, 91.8] (n=126) | 6.8% [-0.9, 14.5] |
| Modified Intent-to-Treat ^b | 87.7% [82.2, 93.2] (n=138) | 83.2% [77.0, 89.5] (n=137) | 4.5% [-3.9, 12.8] |

*OBMT: Omeprazole + PYLERA (bismuth subcitrate potassium / metronidazole / tetracycline hydrochloride)

** OAC: Omeprazole + amoxicillin + clarithromycin

^a Patients were included in the PP analysis if they had *H. pylori* infection documented at baseline, defined as a positive ¹³C-UBT plus histology or culture, had at least one endoscopically verified duodenal ulcer ≥ 0.3 cm at baseline or had a documented history of duodenal ulcer disease, and were not protocol violators. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the evaluable analysis as failures of therapy.

^b Patients were included in the MITT analysis if they had documented *H. pylori* infection at baseline as defined above, and had at least one documented duodenal ulcer at baseline or had a documented history of duodenal ulcer disease, and took at least one dose of study medication. All dropouts were included as failures of therapy.

^c Results for OAC treatment represent all isolates regardless of clarithromycin susceptibility. Eradication rates for clarithromycin susceptible organisms, as defined by an MIC ≤ 0.25 mcg/mL, were 94.6% and 92.1% for the PP and MITT analysis, respectively. Eradication rates for clarithromycin non-susceptible organisms, as defined by an MIC ≥ 0.5 mcg/mL, were 23.1% and 21.4% for the PP and MITT analysis, respectively.

15 REFERENCES

1. Clinical and Laboratory Standards Institute, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Tenth Edition*. CLSI Document M7-A9 [2015], Clinical and Laboratory Standards Institute, 950 West Valley Rd., Suite 2500, Wayne, PA, 19087-1898.
2. Clinical and Laboratory Standards Institute, *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline—Third Edition*. CLSI Document M45- A3 [2016]. Clinical and Laboratory Standards Institute, 950 West Valley Rd., Suite 2500, Wayne, PA. 19087- 1898.

16. HOW SUPPLIED/STORAGE AND HANDLING

PYLERA is supplied as a white opaque capsule containing 140 mg bismuth subcitrate potassium, 125 mg metronidazole, and 125 mg tetracycline hydrochloride, with the APTALISTM logo printed on the body and “BMT” printed on the cap. PYLERA capsules are supplied as bottles of 120 capsules and as the 10 day Therapy pack containing 10 blister cards, with each card containing 12 PYLERA capsules for a total of 120 capsules.

NDC Number: 58914-601-21, Bottles of 120.

NDC Number: 58914-601-20, Blister pack of 120.

Storage

Store at controlled room temperature [68° to 77°F or 20° to 25°C].

17 PATIENT COUNSELING INFORMATION

Lactation

Advise the lactating women to pump and discard their milk during treatment with PYLERA and for 2 days after the therapy ends [see [Use in Specific Populations \(8.2\)](#)].

Hypersensitivity

Inform patients that PYLERA may cause allergic reactions and to discontinue PYLERA at the first sign of urticaria, erythematous rash, flushing, and fever or other symptoms of an allergic reaction [see [Contraindications \(4.5\)](#)].

Central Nervous System Effects

Inform patients of the risk of central and peripheral nervous system effects with PYELRA and to discontinue PYLERA and report immediately to their health-care provider if any neurologic symptoms occur [see [Warnings and Precautions \(5.5\)](#)].

Photosensitivity

Avoid exposure to sun or sun lamps while taking PYLERA [see [Warnings and Precautions \(5.7\)](#)].

Drug Interactions

Advise patients to report to their health-care provider the use of any other medications while taking PYLERA. The administration of any of the following drugs with PYLERA may result in clinically significant adverse reactions or insufficient drug efficacies [see [Contraindications \(4\)](#) and [Drug Interactions \(7\)](#)]:

- Methoxyflurane
- Disulfiram
- Alcoholic Beverages, or Products Containing Propylene Glycol
- Oral Contraceptives
- Anticoagulants
- Lithium
- Antacids, Multivitamins, or Dairy Products
- Busulfan
- Cimetidine
- Phenytoin and Phenobarbital

Darkening of the Tongue and/or Stool

Inform patients that PYLERA may cause temporary and harmless darkening of the tongue and/or black stool generally reversible within several days after treatment is stopped. Stool darkening should not be confused with melena (blood in the stool) [see [Warnings and Precautions \(5.8\)](#)].

Dosing Information

Inform patients that each dose of PYLERA includes 3 capsules. All 3 capsules should be taken 4 times a day (after meals and at bedtime) for 10 days. One omeprazole 20 mg capsule should be taken twice a day with PYLERA after the morning and evening meal for 10 days.

If a dose is missed, advise patient not to make up the dose, but to continue the normal dosing schedule until medication is gone. Patients should not take double doses. If more than 4 doses are missed, advise the patient to contact their health-care provider [see [Dosage and Administration \(2\)](#)].

Administration with Fluids

Instruct patients to swallow the PYLERA capsules whole with a full glass of water (8 ounces). Ingestion of adequate amounts of fluid, particularly with the bedtime dose, is recommended to reduce the risk of esophageal irritation and ulceration by tetracycline hydrochloride [see [Dosage and Administration \(2\)](#)].

Antibacterial Resistance

Patients should be counseled that antibacterial drugs including PYLERA should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When PYLERA is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by PYLERA or other antibacterial drugs in the future.

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