PYLERA™ Capsules

(bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride)

140 mg/125 mg/125 mg

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.

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.

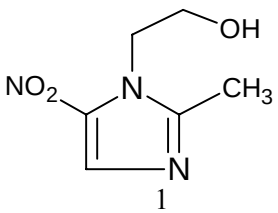
DESCRIPTION

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

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

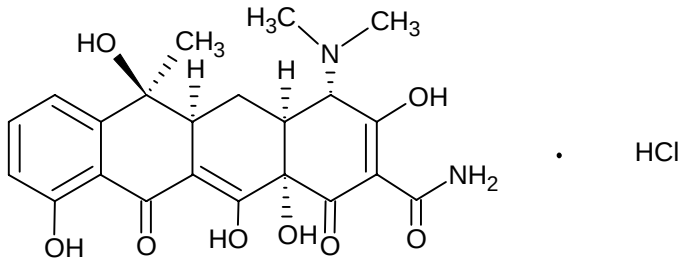
Bismuth subcitrate potassium is a white or almost white powder. It is a soluble, complex bismuth salt of citric acid. The schematized empirical molecular formula of bismuth subcitrate potassium is $Bi(Citrate)_2K_5 \bullet 3\ H_2O$. The equivalent theoretical molecular formula is $BiC_{12}H_{14}K_5O_{17}$. 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 $C_6H_9N_3O_3$ and the following structural formula:



Molecular weight: 171.2

Tetracycline hydrochloride is a yellow, odorless, crystalline powder. Tetracycline 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 $C_{22}H_{24}N_2O_8 \bullet HCl$ and the following structural formula:



Molecular weight: 480.90

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

Bismuth Subcitrate Potassium (Bismuth)

Orally absorbed bismuth is distributed throughout the entire body. Bismuth is highly bound to plasma proteins (>90%). 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 μg/mL) suggesting tissue accumulation and slow elimination.

Metronidazole

Following oral administration, metronidazole is well absorbed, with peak plasma concentrations occurring between 1 and 2 hours after administration. Plasma concentrations of metronidazole are proportional to the administered dose, with oral administration of 500 mg producing a peak plasma concentration of 12 μg/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 concentrations similar to those found in plasma.

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/1.73 m^2.

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

Tetracycline 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 a biologically active form.

Tetracycline is distributed into most body tissues and fluids. It is distributed into the bile and undergoes varying degrees of enterohepatic recirculation. Tetracycline 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

The clinical significance of systemic, as compared to local, drug concentrations for antimicrobial activity against *Helicobacter pylori*, has not been established. A comparative bioavailability study of metronidazole (375 mg), tetracycline (375 mg) and bismuth subcitrate potassium (420 mg, equivalent to 120 mg Bi_2O_3) 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 1.

Table 1. Mean (%CV) Pharmacokinetic Parameters for Metronidazole, Tetracycline, 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	9044.7 (20)	80289 (15)	81849 (16)
	PYLERA™*	8666.3 (22)	83018 (17)	84413 (17)
Tetracycline	Tetracycline Capsules	748.0 (40)	9544 (55)	9864 (53)
	PYLERA™*	773.8 (47)	9674 (50)	9987 (49)
Bismuth	Bismuth Capsule	21.3 (123)	46.5 (129)	65.4 (113)
	PYLERA™*	16.7 (202)	42.5 (191)	56.5 (178)

*PYLERA™ given as a single dose of 3 capsules
**C.V. – Coefficient Variation

The pharmacokinetic parameters for metronidazole, tetracycline and bismuth were also determined when PYLERA™ was administered under fasting and fed conditions, as shown in Table 2. Food reduced the systemic absorption of all three PYLERA™ components, with AUC values for metronidazole, tetracycline 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. (See **DOSAGE AND ADMINISTRATION**)

Table 2. 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	515.8	1.7	8666.3	773.8	16.7

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

*PYLERA™ given as a single dose of 3 capsules

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

Omeprazole Capsules

The effect of omeprazole on bismuth absorption was assessed in 34 healthy volunteers given PYLERA™ (qid) with or without omeprazole (20 mg bid) 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 3). 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 C_{max} concentrations above 50 ng/mL is associated with neurotoxicity.

Table 3. 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 qid for 6 days with or without 20 mg omeprazole bid

**C.V. – Coefficient Variation

Microbiology

The ingredients in PYLERA™ capsules are active as antibacterial agents. Tetracycline hydrochloride interacts with the 30S subunit of the bacterial ribosome and inhibits protein synthesis. Metronidazole is metabolized through reductive pathways into reactive intermediates that have cytotoxic action. The antibacterial action of bismuth salts is not well understood.

PYLERA™ plus omeprazole therapy has been shown to be active against most strains of *Helicobacter pylori in vitro,* and in clinical infections as described in the **CLINICAL STUDIES** and **INDICATIONS AND USAGE** sections.

Susceptibility Testing for *Helicobacter pylori*

Susceptibility testing of *Helicobacter pylori* isolates was performed for metronidazole using agar dilution methodology according to CLSI[1] guidelines and minimum inhibitory concentrations (MICs) were determined.

Susceptibility testing of *Helicobacter pylori* for metronidazole has not been standardized. No interpretive criteria have been established for testing metronidazole against *H. pylori*.

The clinical significance of metronidazole MIC values against *H. pylori* is unknown. In the North American study, pre-treatment metronidazole MIC values showed no correlation with clinical outcome in patients treated with PYLERA™ and omeprazole therapy.

INDICATIONS AND USAGE

PYLERA™ capsules (bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride), 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. (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**)

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 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.

CLINICAL STUDIES

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.

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 breakfast and supper (**OBMT**).

- Clarithromycin 500 mg plus 1000 mg amoxicillin plus 20 mg omeprazole twice a day before breakfast and supper (**OAC**).

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

Table 4. *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 / tetraycyline HCl)

** **OAC**: Omeprazole + Amoxicillin + Clarithromycin

[a] Patients were included in the analysis if they had *H. pylori* infection documented at baseline, defined as a positive ^{13}C-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 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 μg/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 μg/mL, were 23.1% and 21.4% for the PP and MITT analysis, respectively.[1]

CONTRAINDICATIONS

PYLERA™ 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 subcitrate potassium, metronidazole or other nitroimidazole derivatives, or tetracyclines. (See **WARNINGS** and **PRECAUTIONS**)

WARNINGS

Bismuth-containing Products

There have been rare reports of neurotoxicity associated with excessive doses of various bismuth-containing products. 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.

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 PYLERA™ CAPSULES. THEREFORE, PYLERA™ CAPSULES SHOULD NOT BE USED IN THESE PATIENT POPULATIONS. (See **CONTRAINDICATIONS**)

Tetracycline hydrochloride should not be used during pregnancy (see **WARNINGS** above about use during tooth development). 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 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 tetracycline. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs. Treatment should be discontinued at the first evidence of skin erythema.

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

PRECAUTIONS

General

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

Bismuth-containing Products

Bismuth subcitrate potassium and other bismuth-containing products may cause a temporary and harmless darkening of the tongue and/or black stool. Stool darkening must not be confused with melena.

Metronidazole

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

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

Tetracycline

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

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

Information for Patients

- Each dose of PYLERA™ includes 3 capsules. Each dose of all 3 capsules should be taken 4 times a day, after meals and at bedtime for 10 days. Patients should be instructed to swallow the PYLERA™ capsules whole with a full glass of water (8 ounces). One omeprazole 20 mg capsule should be taken twice a day with PYLERA™ after the morning and evening meal for 10 days.

  Daily Dosing Schedule for PYLERA™ and Omeprazole:

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

- Administration of adequate amounts of fluid, particularly with the bedtime dose of PYLERA™, is recommended to reduce the risk of esophageal irritation and ulceration, which can be associated with tetracycline hydrochloride.

- Concurrent use of tetracyclines may render oral contraceptives less effective. Patients should be advised to use a different or additional form of contraception. Breakthrough bleeding has been reported. Women who become pregnant while taking PYLERA™, which contains tetracycline hydrochloride, should be advised to notify their prescriber immediately. (See **CONTRAINDICATIONS** and **WARNINGS**)

- Patients taking PYLERA™, which contains tetracycline hydrochloride, should be cautioned to avoid exposure to sun or sun lamps. (See **WARNINGS**)

- Alcoholic beverages should be avoided while taking PYLERA™, which contains metronidazole, and for at least one day afterward. (See **Drug Interactions**)

- Bismuth subcitrate potassium, contained in PYLERA™, may cause temporary and harmless darkening of the tongue and/or black stool. Stool darkening should not be confused with melena (blood in the stool).

- 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.

Drug Interactions

Interactions with Metronidazole

Lithium

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.

Alcohol

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. Since some pharmaceutical products may contain alcohol, caution should be exercised in patients taking these medications. 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.

Anticoagulants

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. Therefore, frequent monitoring therapy with appropriate adjustment of the anticoagulant dosage is warranted with initiation of PYLERA™.

Cimetidine, Phenytoin, or Phenobarbital

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 this situation.

Interactions with Tetracycline

Methoxyflurane and Tetracycline

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

Oral Contraceptives and Tetracycline

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 PYLERA™ should be advised to notify their prescriber immediately.

Anticoagulants

Tetracycline has been shown to depress plasma prothrombin activity. Therefore, frequent monitoring of anticoagulant therapy with appropriate adjustment of the anticoagulant dosage is warranted with initiation of PYLERA™.

Penicillin

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.

Antacids, Multivitamins, or Dairy Products

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium; preparations containing iron, zinc, or sodium bicarbonate; or milk or dairy products. 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. PYLERA™ should be given after meals and at bedtime, in combination with omeprazole twice a day. (See **DOSAGE AND ADMINISTRATION**)

Bismuth

There is an anticipated reduction in tetracycline systemic absorption due to an interaction with bismuth. 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.

Drug/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 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

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

Bismuth Subcitrate Potassium

No carcinogenicity or reproductive toxicity studies have been conducted with bismuth subcitrate potassium. Bismuth subcitrate potassium 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 1.4 times the indicated human dose for a 50 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.

Metronidazole, at doses up to 400 mg/kg/day (approximately 2 times the indicated 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.

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.

Pregnancy

Teratogenic Effects. Pregnancy Category D

Category D is based on the pregnancy category for tetracycline hydrochloride. (See **CONTRAINDICATIONS** and **WARNINGS/Tetracycline** subsections)

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 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. There are no adequate and well-controlled studies in pregnant women.

Non-teratogenic Effects

Pregnant women with renal disease may be more prone to develop tetracycline-associated liver failure. (See **WARNINGS**)

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. Metronidazole is secreted in human milk in concentrations similar to those found in plasma. 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. (See **CONTRAINDICATIONS**)

Pediatric Use

Tetracycline use in children may cause permanent discoloration of the teeth. Enamel hypoplasia has also been reported. PYLERA™ should not be used in children less than 8 years of age. Safety and effectiveness of PYLERA™ in pediatric patients infected with *Helicobacter pylori* have not been established. (See **CONTRAINDICATIONS** and **WARNINGS**)

Geriatric Use

Of the 324 patients who received PYLERA™ in clinical studies, 40 were ≥ 65 years old. Clinical studies of PYLERA™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing PYLERA™. As stated in the **CONTRAINDICATIONS** section, PYLERA™ is contraindicated in patients with renal or hepatic impairment.

ADVERSE REACTIONS

The safety of PYLERA™ plus omeprazole for 10 days to eradicate *Helicobacter pylori* was evaluated in 324 patients (aged 18 to 75 years) in two clinical trials world-wide. One trial was conducted in the US and Canada (North American Trial). The other trial was conducted in Europe, Australia, Canada and the US (International Trial).

In the North American trial, patients with a duodenal ulcer or history of an ulcer were randomized to PYLERA™ plus omeprazole (OBMT) or omeprazole, amoxicillin, and

clarithromycin (OAC). The International trial differed from the North American trial in that there was no comparator group and all patients received OBMT. Also, patients enrolled in the International trial all had gastrointestinal symptoms (i.e., non-ulcer dyspepsia). It was not necessary for these patients to have a history or current duodenal ulcer.

Two hundred and ninety-nine (299) patients (147 OBMT and 152 OAC) were exposed to at least one dose of the study drugs in the North American trial. Of these patients, 86/147 (58.5%) in the OBMT group and 90/152 (59.2%) in the OAC group reported adverse events. In the OBMT group there were 212 events reported and 236 events reported in the OAC group. An adverse event was defined as any event not present prior to exposure to study medication or any event present at study entry that worsens in either intensity or frequency following exposure to study medication.

The most frequent adverse events (incidence >1%) by treatment group from the North American trial in order of decreasing incidence for the OBMT group are shown below in Table 5. For both treatments, gastrointestinal adverse events (e.g., diarrhea, dyspepsia, abdominal pain, and nausea) are the most commonly reported.

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 or another drug and may not reflect the rates observed in practice.

Table 5. Adverse Events of Incidence > 1% in Controlled Clinical Trial By Treatment Group, By Decreasing Frequency [n (%)]

Preferred Term	OBMT* (n = 147)	OAC** (n = 152)
Stool Abnormality	23 (15.6)	7 (4.6)
Diarrhea	13 (8.8)	23 (15.1)
Dyspepsia	13 (8.8)	17 (11.2)
Abdominal Pain	13 (8.8)	15 (9.9)
Nausea	12 (8.2)	16 (10.5)
Headache	12 (8.2)	11 (7.2)
Flu Syndrome	8 (5.4)	5 (3.3)
Taste Perversion	7 (4.8)	18 (11.8)
Asthenia	6 (4.1)	4 (2.6)
Vaginitis	6 (4.1)	4 (2.6)
Dizziness	5 (3.4)	4 (2.6)
Lab Test Abnormality	4 (2.7)	4 (2.6)
Pain	3 (2.0)	7 (4.6)
Infection	3 (2.0)	5 (3.3)
Pharyngitis	3 (2.0)	4 (2.6)
Pain Back	3 (2.0)	2 (1.3)
SGPT Increased	3 (2.0)	0
Urinary abnormality	3 (2.0)	0
Infection	2 (1.4)	6 (3.9)
Rhinitis	2 (1.4)	4 (2.6)
Dry Mouth	2 (1.4)	1 (0.7)
Vomit	2 (1.4)	1 (0.7)
Anxiety	2 (1.4)	0
Gastritis	2 (1.4)	0
Gastroenteritis	2 (1.4)	0
Pain, Chest	2 (1.4)	0
Palpitation	2 (1.4)	0
Rash Maculo-Papular	2 (1.4)	0
SGOT Increase	2 (1.4)	0
Flatulence	1 (0.7)	6 (3.9)
Cough	1 (0.7)	3 (2.0)
Rash	1 (0.7)	3 (2.0)
Sinusitis	1 (0.7)	2 (1.3)
Pruritis	0	4 (2.6)
Glossitis	0	2 (1.3)

*OBMT = Omeprazole+PYLERA™ (bismuth subcitrate potassium/metronidazole /tetracycline HCl);
OAC = Omeprazole+Amoxicillin+Clarithromycin

The following selected adverse reactions from the labeling for bismuth subsalicylate, a similar bismuth-containing product to bismuth subcitrate potassium, are provided for information.

Gastrointestinal: black stools

Mouth: temporary and harmless darkening of the tongue

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

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: 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.

Other: 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. Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported.

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

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

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

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

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

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

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 has been reported rarely. (See **WARNINGS**)

OVERDOSAGE

In case of an overdose, patients should contact a physician, poison control center, or emergency room. There is neither a pharmacological basis nor data suggesting an increased toxicity of the combination compared to individual components.

DOSAGE AND ADMINISTRATION

Each dose of PYLERA™ includes 3 capsules. Each dose of all 3 capsules should be taken 4 times a day, after meals and at bedtime for 10 days. Patients should be instructed to swallow the PYLERA™ capsules whole with a full glass of water (8 ounces). One omeprazole 20 mg capsule should be taken twice a day with PYLERA™ after the morning and evening meal for 10 days.

Table 6: Daily Dosing Schedule for PYLERA™ and Omeprazole

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

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.

HOW SUPPLIED

PYLERA™ is supplied as a white opaque capsule containing 140 mg bismuth subcitrate potassium, 125 mg metronidazole, and 125 mg tetracycline hydrochloride, with Axcan Pharma logo printed on body and BMT printed on cap. PYLERA™ is supplied in bottles of 120 capsules.

NDC Number 58914-600-21, Bottle of 120.

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

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656 ## REFERENCES

657

658 1. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial*
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CAUTION: Federal law prohibits dispensing without a prescription.

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