

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-786

APPROVED LABELING

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PYLERA™ Capsules
(biscalcitrates, 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.

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DESCRIPTION

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

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- 14 - biscalcitrates, 140 mg
- 15 - metronidazole, 125 mg
- 16 - smaller capsule (size 3) containing tetracycline hydrochloride, 125 mg

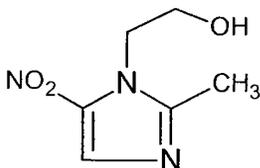
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Biscalcitrates is a white or almost white powder. It is a soluble, complex bismuth salt of citric acid. The schematized empirical molecular formula of biscalcitrates is $\text{Bi}(\text{Citrate})_2\text{K}_5 \cdot 3 \text{H}_2\text{O}$. The equivalent 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 biscalcitrates is 834.71.

18

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:

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Molecular weight: 171.2

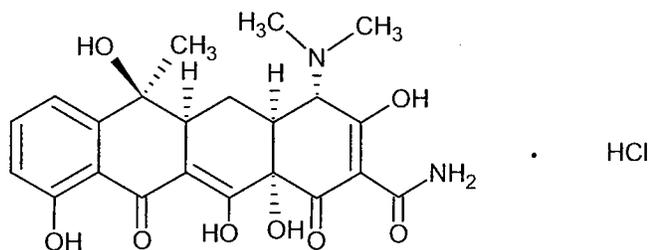
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34 Tetracycline hydrochloride is a yellow, odorless, crystalline powder. Tetracycline is
35 stable in air, but exposure to strong sunlight causes it to darken. Tetracycline
36 hydrochloride is (4S,4aS,5aS,6S,12aS)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-
37 octahydro-3,6,10,12,12a-penta-hydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide
38 hydrochloride, with a molecular formula of $C_{22}H_{24}N_2O_8 \cdot HCl$ and the following structural
39 formula:

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Molecular weight: 480.90

45

46 Each PYLERA™ capsule contains the following inactive ingredients: Magnesium
47 Stearate NF, Lactose Monohydrate NF, and Talc USP.

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CLINICAL PHARMACOLOGY

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Pharmacokinetics

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The pharmacokinetics of the individual components of PYLERA™, biscalcitrates, 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.

52

53

Biscalcitrates (Bismuth)

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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

55

56

63 two weeks after discontinuation (urine drug concentrations 24 to 250 µg/mL) suggesting
64 tissue accumulation and slow elimination.

65

66 Metronidazole

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

71

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

77

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

86

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

90

91 Tetracycline Hydrochloride

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

97

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

103

104 PYLERA™ Capsules

105 The clinical significance of systemic, as compared to local, drug concentrations for
 106 antimicrobial activity against *Helicobacter pylori*, has not been established. A
 107 comparative bioavailability study of metronidazole (375 mg), tetracycline (375 mg) and
 108 bismuth (420 mg, equivalent to 120 mg Bi₂O₃) administered as PYLERA™ or as 3
 109 separate capsule formulations administered simultaneously was conducted in healthy
 110 male volunteers. The pharmacokinetic parameters for the individual drugs when
 111 administered as separate capsule formulations or as PYLERA™ are similar, as shown in
 112 Table 1.

113

114 **Table 1. Mean (%CV) Pharmacokinetic Parameters for Metronidazole, Tetracycline, and**
 115 **Bismuth 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)

116 *PYLERA™ given as a single dose of 3 capsules

117 **C.V. – Coefficient Variation

118

119 The pharmacokinetic parameters for metronidazole, tetracycline and bismuth were also
 120 determined when PYLERA™ was administered under fasting and fed conditions, as
 121 shown in Table 2. Food reduced the systemic absorption of all three PYLERA™
 122 components, with AUC values for metronidazole, tetracycline and bismuth being reduced
 123 by 6%, 34% and 60%, respectively. Reduction in the absorption of all three PYLERA™
 124 components in the presence of food is not considered to be clinically significant.
 125 PYLERA™ should be given after meals and at bedtime, in combination with omeprazole
 126 twice a day. (See **DOSAGE AND ADMINISTRATION**)

127

128 **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)

129 *PYLERA™ given as a single dose of 3 capsules

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

131

132 Omeprazole Capsules

133 The effect of omeprazole on bismuth absorption was assessed in 34 healthy volunteers
 134 given PYLERA™ (qid) with or without omeprazole (20 mg bid) for 6 days. In the
 135 presence of omeprazole, the extent of absorption of bismuth from PYLERA™ was
 136 significantly increased, compared to when no omeprazole was given (Table 2).
 137 Concentration-dependent neurotoxicity is associated with long-term use of bismuth and
 138 not likely to occur with short-term administration or at steady state concentrations below
 139 50 ng/mL. One subject transiently achieved a maximum bismuth concentration (C_{max})
 140 higher than 50 ng/mL (73 ng/mL) following multiple dosing of PYLERA™ with
 141 omeprazole. The patient did not exhibit symptoms of neurotoxicity during the study.
 142 There is no clinical evidence to suggest that short-term exposure to C_{max} concentrations
 143 above 50 ng/mL is associated with neurotoxicity.

144

145 **Table 3. Mean Bismuth Pharmacokinetic Parameters following PYLERA™**
 146 **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

147 *PYLERA™ given as 3 capsules qid for 6 days with or without 20 mg omeprazole bid

148 **C.V. – Coefficient Variation

149

150 **Microbiology**

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

156

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

160

161 Susceptibility Testing for *Helicobacter pylori*

162 Susceptibility testing of *Helicobacter pylori* isolates was performed for metronidazole
163 using agar dilution methodology according to CLSI¹ guidelines and minimum inhibitory
164 concentrations (MICs) were determined.

165

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

168

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

173

174

INDICATIONS AND USAGE

175 PYLERA™ capsules (bismuth citrate, metronidazole, and tetracycline hydrochloride), in
176 combination with omeprazole are indicated for the treatment of patients with
177 *Helicobacter pylori* infection and duodenal ulcer disease (active or history of within the
178 past 5 years) to eradicate *H. pylori*. The eradication of *Helicobacter pylori* has been
179 shown to reduce the risk of duodenal ulcer recurrence. (See **CLINICAL STUDIES** and
180 **DOSAGE AND ADMINISTRATION**)

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

188

189

CLINICAL STUDIES

190

191 **Eradication of *Helicobacter pylori* in Patients with Active Duodenal Ulcer or** 192 **History of Duodenal Ulcer Disease**

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

196

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

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201

- Three (3) PYLERA™ capsules four times daily, after meals and at bedtime plus 20 mg omeprazole twice a day after breakfast and supper (OBMT).

202

203

204

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

205

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209

H. pylori eradication rates, defined as two negative ¹³C-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.

210

211

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]

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213

214

* OBMT: Omeprazole + PYLERA™ (bismuth citrate / metronidazole / tetracycline HCl)
** OAC: Omeprazole + Amoxicillin + Clarithromycin

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^a Patients were included in the 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.

221

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225

^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.

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^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

232 **CONTRAINDICATIONS**

233
234 PYLERA™ therapy is contraindicated in pregnant or nursing women, pediatric patients,
235 in patients with renal or hepatic impairment, and in those with known hypersensitivity to
236 biscalcitrates, metronidazole or other nitroimidazole derivatives, or tetracyclines. (See
237 **WARNINGS** and **PRECAUTIONS**)

238
239
240 **WARNINGS**

241
242 **Bismuth-containing Products**

243 There have been rare reports of neurotoxicity associated with excessive doses of various
244 bismuth-containing products. Effects have been reversible with discontinuation of
245 therapy.

246
247 **Metronidazole**

248 Central Nervous System Effects

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

256
257 **Tetracycline**

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

267
268 Tetracycline hydrochloride should not be used during pregnancy (see **WARNINGS**
269 above about use during tooth development). Results of animal studies indicate that
270 tetracycline crosses the placenta, is found in fetal tissues, and can have toxic effects on
271 the developing fetus (often related to retardation of skeletal development). Evidence of
272 embryotoxicity has also been noted in animals treated early in pregnancy. If this drug is

273 used during pregnancy or if the patient becomes pregnant while taking this drug, the
274 patient should be apprised of the potential hazard to the fetus.

275

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

280

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

285

286 PRECAUTIONS

287

288 **General**

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

292

293 Bismuth-containing Products

294 Bismuth-containing products may cause a temporary and harmless
295 darkening of the tongue and/or black stool. Stool darkening must not be confused with
296 melena.

297

298 Metronidazole

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

305

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

308

309 Tetracycline

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

313

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

318

319 **Information for Patients**

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

325

326 Daily Dosing Schedule for PYLERA™ and Omeprazole:

327

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

328

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

332

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

339

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

342

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

345

- 346 • Biskalcitrate, contained in PYLERA™, may cause temporary and harmless
347 darkening of the tongue and/or black stool. Stool darkening should not be
348 confused with melena (blood in the stool).

349

350

- 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.

351

352

353

354

355 **Drug Interactions**

356

357 **Interactions with Metronidazole**

358

359 **Lithium**

360

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.

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362

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365

366 **Alcohol**

367

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.

368

369

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375 **Anticoagulants**

376

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™.

377

378

379

380

381 **Cimetidine, Phenytoin, or Phenobarbital**

382

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.

383

384

385

386

387

388

389 **Interactions with Tetracycline**

390

391 Methoxyflurane and Tetracycline

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

394

395 Oral Contraceptives and Tetracycline

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

400

401 Anticoagulants

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

405

406 Penicillin

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

410

411 Antacids, Multivitamins, or Dairy Products

412 Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or
413 magnesium; preparations containing iron, zinc; or sodium bicarbonate; or milk or dairy
414 products. The clinical significance of reduced tetracycline systemic exposure is unknown
415 as the relative contribution of systemic versus local antimicrobial activity against
416 *Helicobacter pylori* has not been established. PYLERA™ should be given after meals
417 and at bedtime, in combination with omeprazole twice a day. (See **DOSAGE AND**
418 **ADMINISTRATION**)

419

420 Bismuth

421 There is an anticipated reduction in tetracycline systemic absorption due to an interaction
422 with bismuth. The clinical significance of reduced tetracycline systemic exposure is
423 unknown as the relative contribution of systemic versus local antimicrobial activity
424 against *Helicobacter pylori* has not been established.

425

426 **Drug/Laboratory Test Interactions**

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

429

430 Biskalcitrate may cause a temporary and harmless darkening of the stool. However, this
431 does not interfere with standard tests for occult blood.

432

433 Metronidazole may interfere with certain types of determinations of serum chemistry
434 values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase
435 (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose.
436 Values of zero may be observed. All of the assays in which interference has been
437 reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide
438 (NAD+ \rightleftharpoons NADH). Interference is due to the similarity in absorbance peaks of NADH
439 (340 nm) and metronidazole (322 nm) at pH 7.

440

441 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

442 No long-term studies have been performed to evaluate the effect of the combined use of
443 biskalcitrate, metronidazole, and tetracycline on carcinogenesis, mutagenesis, or
444 impairment of fertility.

445

446 Biskalcitrate

447 No carcinogenicity or reproductive toxicity studies have been conducted with
448 biskalcitrate. Biskalcitrate did not show mutagenic potential in the NTP *Salmonella* plate
449 assay.

450

451 Metronidazole

452 Metronidazole has shown evidence of carcinogenic activity in a number of studies
453 involving chronic, oral administration in mice and rats. Prominent among the effects in
454 the mouse was an increased incidence of pulmonary tumorigenesis. This has been
455 observed in all six reported studies in that species, including one study in which the
456 animals were dosed on an intermittent schedule (administration during every fourth week
457 only). At the highest dose levels, (approximately 500 mg/kg/day, which is approximately
458 1.4 times the indicated human dose for a 50 kg adult based on body surface area), there
459 was a statistically significant increase in the incidence of malignant liver tumors in male
460 mice. Also, the published results of one of the mouse studies indicate an increase in the
461 incidence of malignant lymphomas as well as pulmonary neoplasms associated with
462 lifetime feeding of the drug. All these effects are statistically significant. Long-term, oral-
463 dosing studies in the rat showed statistically significant increases in the incidence of
464 various neoplasms, particularly in mammary and hepatic tumors, among female rats
465 administered metronidazole over those noted in the concurrent female control groups.
466 Two lifetime tumorigenicity studies in hamsters have been performed and reported to be
467 negative.

468

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

472

473 Metronidazole, at doses up to 400 mg/kg/day (approximately 2 times the indicated human
474 dose based on mg/m^2) for 28 days, failed to produce any adverse effects on fertility and
475 testicular function in male rats. Fertility studies have been performed in mice at doses up
476 to six times the maximum recommended human dose based on mg/m^2 and have revealed
477 no evidence of impaired fertility.

478

479 Tetracycline hydrochloride

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

483

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

487

488 Tetracycline hydrochloride had no effect on fertility when administered in the diet to
489 male and female rats at a daily intake of 25 times the human dose.

490

491 **Pregnancy**

492 Teratogenic Effects. Pregnancy Category D

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

495

496 Metronidazole crosses the placental barrier and its effects on the human fetal
497 organogenesis are not known. No fetotoxicity was observed when metronidazole was
498 administered orally to pregnant mice at 20 mg/kg/day, approximately 5 percent of the
499 indicated human dose (1500 mg/day) based on body surface area; however, in a single
500 small study where the drug was administered intraperitoneally, some intrauterine deaths
501 were observed. The relationship of these findings to the drug is unknown. There are no
502 adequate and well-controlled studies in pregnant women.

503

504 Non-teratogenic Effects

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

507

508 **Labor and Delivery**

509 The effect of this therapy on labor and delivery is unknown.

510

511 **Nursing Mothers**

512 Metronidazole and tetracycline are both secreted into human milk. Metronidazole is
513 secreted in human milk in concentrations similar to those found in plasma. Because of the
514 potential for tumorigenicity shown for metronidazole in mouse and rat studies, and
515 because of the potential for serious adverse reactions in nursing infants from
516 tetracyclines, a decision should be made whether to discontinue nursing or to discontinue
517 therapy, taking into account the importance of the therapy to the mother. (See
518 **CONTRAINDICATIONS**)

519

520 **Pediatric Use**

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

526

527 **Geriatric Use**

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

537

538

ADVERSE REACTIONS

539

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

544

545 In the North American trial, patients with a duodenal ulcer or history of an ulcer were
546 randomized to PYLERA™ plus omeprazole (OBMT) or omeprazole, amoxicillin, and
547 clarithromycin (OAC). The International trial differed from the North American trial in
548 that there was no comparator group and all patients received OBMT. Also, patients
549 enrolled in the International trial all had gastrointestinal symptoms (i.e., non-ulcer
550 dyspepsia). It was not necessary for these patients to have a history or current duodenal
551 ulcer.

552

553 Two hundred and ninety-nine (299) patients (147 OBMT and 152 OAC) were exposed to
554 at least one dose of the study drugs in the North American trial. Of these patients, 86/147
555 (58.5%) in the OBMT group and 90/152 (59.2%) in the OAC group reported adverse
556 events. In the OBMT group there were 212 events reported and 236 events reported in the
557 OAC group. An adverse event was defined as any event not present prior to exposure to
558 study medication or any event present at study entry that worsens in either intensity or
559 frequency following exposure to study medication.

560

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

565

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

569 **Table 5. Adverse Events of Incidence > 1% in Controlled Clinical Trial By Treatment**
570 **Group, By Decreasing Frequency [n (%)]**
571

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™ (biscalcitrates/metronidazole/tetracycline HCl);
OAC = Omeprazole+Amoxicillin+Clarithromycin

572
573
574

575 *The following selected adverse reactions from the labeling for bismuth subsalicylate, a*
576 *similar bismuth-containing product to bismuth citrate, are provided for information.*

577 **Gastrointestinal:** black stools

578 **Mouth:** temporary and harmless darkening of the tongue

579

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

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

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

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

587 **CNS:** Two serious adverse reactions reported in patients treated with metronidazole have
588 been convulsive seizures and peripheral neuropathy, the latter characterized mainly by
589 numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been
590 reported in some patients receiving prolonged administration of metronidazole, patients
591 should be specifically warned about these reactions and should be told to stop the drug
592 and report immediately to their physicians if any neurologic symptoms occur.

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

595 **Other:** If patients receiving metronidazole drink alcoholic beverages, they may
596 experience abdominal distress, nausea, vomiting, flushing, or headache. A modification
597 of the taste of alcoholic beverages has also been reported. Rare cases of pancreatitis,
598 which abated on withdrawal of the drug, have been reported.

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

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

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

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

610 **Blood:** hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, neutropenia,
611 and eosinophilia

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

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

617 **Skin:** Maculopapular and erythematous rashes have been reported. Exfoliative dermatitis
618 has been rarely reported. Photosensitivity has been reported rarely (see **WARNINGS**).

619

620

OVERDOSAGE

621

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

625

626

DOSAGE AND ADMINISTRATION

627

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

633

634

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

635

636 Ingestion of adequate amounts of fluid, particularly with the bedtime dose, is
637 recommended to reduce the risk of esophageal irritation and ulceration by tetracycline
638 hydrochloride.

639

640

HOW SUPPLIED

641

642 PYLERA™ is supplied as a red opaque capsule containing 140 mg biskalcitrate, 125 mg
643 metronidazole, and 125 mg tetracycline hydrochloride, with Axcan Pharma logo printed
644 on body and HP, diagram of stomach and BMT printed on cap. PYLERA™ is supplied
645 in bottles of 120 capsules.

646

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

648

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

650

651

REFERENCES

652

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656 26, No. 2, CLSI, Wayne, PA, January 2006.

657

658

659 CAUTION: Federal law prohibits dispensing without a prescription.

660

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665 Birmingham, AL 35242

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/s/

Edward Cox

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