

1 (List Nos.: 4317, 4314, 4315)

2

3 **NEW**

4

5 **Zemplar[®]**

6 (paricalcitol) Capsules

7 R_x only

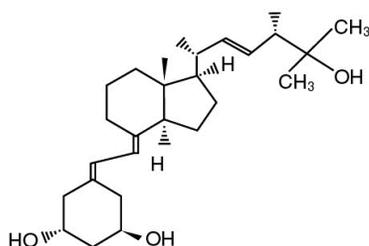
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9 **DESCRIPTION**

10 Paricalcitol, USP, the active ingredient in Zemplar Capsules, is a synthetically
11 manufactured analog of calcitriol, the metabolically active form of vitamin D indicated
12 for the prevention and treatment of secondary hyperparathyroidism in chronic kidney
13 disease. Zemplar is available as soft gelatin capsules for oral administration containing
14 1 microgram, 2 micrograms or 4 micrograms of paricalcitol. Each capsule also contains
15 medium chain triglycerides, alcohol, and butylated hydroxytoluene. The medium chain
16 triglycerides are fractionated from coconut oil or palm kernel oil. The capsule shell is
17 composed of gelatin, glycerin, titanium dioxide, iron oxide red (2 microgram capsules
18 only), iron oxide yellow (2 microgram and 4 microgram capsules), iron oxide black (1
19 microgram capsules only), and water.

20

21 Paricalcitol is a white, crystalline powder with the empirical formula of C₂₇H₄₄O₃, which
22 corresponds to a molecular weight of 416.64. Paricalcitol is chemically designated as
23 19-nor-1 α ,3 β ,25-trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene and has the
24 following structural formula:



25

26

27 **CLINICAL PHARMACOLOGY**

28 Secondary hyperparathyroidism is characterized by an elevation in parathyroid hormone
29 (PTH) associated with inadequate levels of active vitamin D hormone. The source of
30 vitamin D in the body is from synthesis in the skin and from dietary intake. Vitamin D
31 requires two sequential hydroxylations in the liver and the kidney to bind to and to

32 activate the vitamin D receptor (VDR). The endogenous VDR activator, calcitriol
33 [1,25(OH)₂ D₃], is a hormone that binds to VDRs that are present in the parathyroid
34 gland, intestine, kidney, and bone to maintain parathyroid function and calcium and
35 phosphorus homeostasis, and to VDRs found in many other tissues, including prostate,
36 endothelium and immune cells. VDR activation is essential for the proper formation and
37 maintenance of normal bone. In the diseased kidney, the activation of vitamin D is
38 diminished, resulting in a rise of PTH, subsequently leading to secondary
39 hyperparathyroidism and disturbances in the calcium and phosphorus homeostasis.¹
40 Decreased levels of 1,25(OH)₂ D₃ have been observed in early stages of chronic kidney
41 disease. The decreased levels of 1,25(OH)₂ D₃ and resultant elevated PTH levels, both
42 of which often precede abnormalities in serum calcium and phosphorus, affect bone
43 turnover rate and may result in renal osteodystrophy.

44

45 **Mechanism of Action**

46 Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with
47 modifications to the side chain (D₂) and the A (19-nor) ring. Preclinical and *in vitro*
48 studies have demonstrated that paricalcitol's biological actions are mediated through
49 binding of the VDR, which results in the selective activation of vitamin D responsive
50 pathways. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone
51 levels by inhibiting PTH synthesis and secretion.

52

53 **Pharmacokinetics**

54 **Absorption**

55 Paricalcitol is well absorbed. In healthy subjects, following oral administration of
56 paricalcitol at 0.24 mcg/kg, the mean absolute bioavailability was approximately 72%;
57 the mean maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the
58 concentration time curve (AUC_{0-∞}) were 0.630 ng/mL, 3 hours and 5.25 ng•h/mL,
59 respectively. A food effect study in healthy subjects indicated that the C_{max} and AUC_{0-∞}
60 were unchanged when paricalcitol was administered with a high fat meal compared to
61 fasting. Food delays T_{max} about 2 hours. The AUC_{0-∞} of paricalcitol increased
62 proportionally over the dose range of 0.06 to 0.48 mcg/kg in healthy subjects. Following
63 multiple dosing, as once daily in CKD Stage 4 patients, the exposure (AUC) was slightly
64 lower than that obtained after a single dose administration.

65

66 **Distribution**

67 Paricalcitol is extensively bound to plasma proteins (≥99.8%). The mean apparent
68 volume of distribution following a 0.24 mcg/kg dose of paricalcitol in healthy subjects

69 was 34 L. The mean apparent volume of distribution following a 4 mcg dose of
70 paricalcitol in CKD Stage 3 and 3 mcg dose in CKD Stage 4 patients is between 44 and
71 46 L.

72

73 Metabolism

74 After oral administration of a 0.48 mcg/kg dose of ³H-paricalcitol, parent drug was
75 extensively metabolized, with only about 2% of the dose eliminated unchanged in the
76 feces, and no parent drug found in the urine. Several metabolites were detected in both
77 the urine and feces. Most of the systemic exposure was from the parent drug. Two minor
78 metabolites, relative to paricalcitol, were detected in human plasma. One metabolite was
79 identified as 24(R)-hydroxy paricalcitol, while the other metabolite was unidentified.
80 The 24(R)-hydroxy paricalcitol is less active than paricalcitol in an *in vivo* rat model of
81 PTH suppression.

82

83 *In vitro* data suggest that paricalcitol is metabolized by multiple hepatic and non-hepatic
84 enzymes, including mitochondrial CYP24, as well as CYP3A4 and UGT1A4. The
85 identified metabolites include the product of 24(R)-hydroxylation, 24,26- and 24,28-
86 dihydroxylation and direct glucuronidation.

87

88 Elimination

89 Paricalcitol is eliminated primarily via hepatobiliary excretion; approximately 70% of the
90 radiolabeled dose is recovered in the feces and 18% is recovered in the urine. In healthy
91 subjects, the mean elimination half-life of paricalcitol is 4 to 6 hours over the studied
92 dose range of 0.06 to 0.48 mcg/kg. The pharmacokinetics of paricalcitol capsule have
93 been studied in patients with chronic kidney disease (CKD) Stage 3 and 4 patients. After
94 administration of 4 mcg paricalcitol capsule in CKD Stage 3 patients, the mean
95 elimination half-life of paricalcitol is 17 hours. The mean half-life of paricalcitol is 20
96 hours in CKD Stage 4 patients when given 3 mcg of paricalcitol capsule.

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Table 1. Paricalcitol Capsule Pharmacokinetic Characteristics in CKD Stage 3 and 4 Patients

| Pharmacokinetic Parameters | CKD Stage 3 n=15* | CKD Stage 4 n=14* |
|------------------------------|----------------------|----------------------|
| C _{max} (ng/mL) | 0.11 ± 0.04 | 0.06 ± 0.01 |
| AUC _{0-∞} (ng•h/mL) | 2.42 ± 0.61 | 2.13 ± 0.73 |
| CL/F (L/h) | 1.77 ± 0.50 | 1.52 ± 0.36 |
| V/F (L) | 43.7 ± 14.4 | 46.4 ± 12.4 |
| t _{1/2} | 16.8 ± 2.65 | 19.7 ± 7.2 |

100 * Four mcg paricalcitol capsule was given to CKD Stage 3 patients; three mcg paricalcitol capsule was
101 given to CKD Stage 4 patients.

102
103

Special Populations

104
105

Geriatric

106 The pharmacokinetics of paricalcitol have not been investigated in geriatric patients
107 greater than 65 years (see **PRECAUTIONS**).

108
109

Pediatric

110 The pharmacokinetics of paricalcitol have not been investigated in patients less than
111 18 years of age.

112
113

Gender

114 The pharmacokinetics of paricalcitol following single doses over 0.06 to 0.48 mcg/kg
115 dose range were gender independent.

116
117

Hepatic Impairment

118 The disposition of paricalcitol (0.24 mcg/kg) was compared in patients with mild (n = 5)
119 and moderate (n = 5) hepatic impairment (as indicated by the Child-Pugh method) and
120 subjects with normal hepatic function (n = 10). The pharmacokinetics of unbound
121 paricalcitol were similar across the range of hepatic function evaluated in this study. No
122 dosing adjustment is required in patients with mild and moderate hepatic impairment.
123 The influence of severe hepatic impairment on the pharmacokinetics of paricalcitol has
124 not been evaluated.

125

126 *Renal Impairment*

127 Following administration of Zemplar Capsules, the pharmacokinetic profile of
128 paricalcitol for CKD Stage 5 on hemodialysis (HD) or peritoneal dialysis (PD) was
129 comparable to that in CKD 3 or 4 patients. Therefore, no special dosing adjustments are
130 required other than those recommended in the Dosage and Administration section (see
131 **DOSAGE AND ADMINISTRATION**).

132

133 **Drug Interactions**

134 An *in vitro* study indicates that paricalcitol is not an inhibitor of CYP1A2, CYP2A6,
135 CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A at
136 concentrations up to 50 nM (21 ng/mL) (approximately 20-fold greater than that obtained
137 after highest tested dose). In fresh primary cultured hepatocytes, the induction observed
138 at paricalcitol concentrations up to 50 nM was less than two-fold for CYP2B6, CYP2C9
139 or CYP3A, where the positive controls rendered a six- to nineteen-fold induction. Hence,
140 paricalcitol is not expected to inhibit or induce the clearance of drugs metabolized by
141 these enzymes.

142

143 Omeprazole: The pharmacokinetic interaction between paricalcitol capsule (16 mcg) and
144 omeprazole (40 mg; oral) was investigated in a single dose, crossover study in healthy
145 subjects. The pharmacokinetics of paricalcitol were unaffected when omeprazole was
146 administered approximately 2 hour prior to the paricalcitol dose.

147

148 Ketoconazole: The effect of multiple doses of ketoconazole administered as 200 mg BID
149 for 5 days on the pharmacokinetics of paricalcitol capsule has been studied in healthy
150 subjects. The C_{max} of paricalcitol was minimally affected, but $AUC_{0-\infty}$ approximately
151 doubled in the presence of ketoconazole. The mean half-life of paricalcitol was 17.0
152 hours in the presence of ketoconazole as compared to 9.8 hours, when paricalcitol was
153 administered alone (See **PRECAUTIONS**).

154

155 **CLINICAL STUDIES**

156 The safety and efficacy of Zemplar Capsules were evaluated in three, 24-week, double
157 blind, placebo-controlled, randomized, multicenter, Phase 3 clinical studies in CKD Stage
158 3 and 4 patients. Two studies used an identical three times a week dosing design, and
159 one study used a daily dosing design. A total of 107 patients received Zemplar Capsules
160 and 113 patients received placebo. The mean age of the patients was 63 years, 68% were
161 male, 71% were Caucasian, and 26% were African-American. The average baseline iPTH
162 was 274 pg/mL (range: 145-856 pg/mL). The average duration of CKD prior to study

163 entry was 5.7 years. At study entry 22% were receiving calcium based phosphate binders
164 and/or calcium supplements. Baseline 25-hydroxyvitamin D levels were not measured.

165
166 The initial dose of Zemplar Capsules was based on baseline iPTH. If iPTH was
167 ≤ 500 pg/mL, Zemplar Capsules were administered 1 mcg daily or 2 mcg three times a
168 week, not more than every other day. If iPTH was >500 pg/mL, Zemplar Capsules were
169 administered 2 mcg daily or 4 mcg three times a week, not more than every other day.
170 The dose was titrated by 1 mcg daily or 2 mcg three times a week every 2 to 4 weeks
171 until iPTH levels were reduced by at least 30% from baseline. The overall average
172 weekly dose of Zemplar Capsules was 9.6 mcg/week in the daily regimen and
173 9.5 mcg/week in the three times a week regimen.

174
175 In the clinical studies, doses were titrated for any of the following reasons: if iPTH fell to
176 <60 pg/mL, or decreased $>60\%$ from baseline, the dose was reduced or temporarily
177 withheld; if iPTH decreased $<30\%$ from baseline and serum calcium was ≤ 10.3 mg/dL
178 and serum phosphorus was ≤ 5.5 mg/dL, the dose was increased; and if iPTH decreased
179 between 30 to 60% from baseline and serum calcium and phosphorus were ≤ 10.3 mg/dL
180 and ≤ 5.5 mg/dL, respectively, the dose was maintained. Additionally, if serum calcium
181 was between 10.4 to 11.0 mg/dL, the dose was reduced irrespective of iPTH, and the
182 dose was withheld if serum calcium was >11.0 mg/dL. If serum phosphorus was
183 > 5.5 mg/dL, dietary counseling was provided, and phosphate binders could have been
184 initiated or increased. If the elevation persisted, the Zemplar Capsules dose was
185 decreased. Seventy-seven percent (77%) of the Zemplar Capsules treated patients and
186 82% of the placebo treated patients completed the 24-week treatment. The primary
187 efficacy endpoint of at least two consecutive $\geq 30\%$ reductions from baseline iPTH was
188 achieved by 91% of Zemplar Capsules treated patients and 13% of the placebo treated
189 patients ($p<0.001$). The proportion of Zemplar Capsules treated patients achieving two
190 consecutive $\geq 30\%$ reductions was similar between the daily and the three times a week
191 regimens (daily: 30/33, 91%; three times a week: 62/68, 91%).

192
193 The incidences of hypercalcemia (defined as two consecutive serum calcium values
194 >10.5 mg/dL), hyperphosphatemia and elevated Ca x P product in Zemplar Capsules
195 treated patients was similar to placebo. There were no treatment related adverse events
196 associated with hypercalcemia or hyperphosphatemia in the Zemplar Capsules group. No
197 increases in urinary calcium or phosphorous were detected in Zemplar Capsules treated
198 patients compared to placebo.

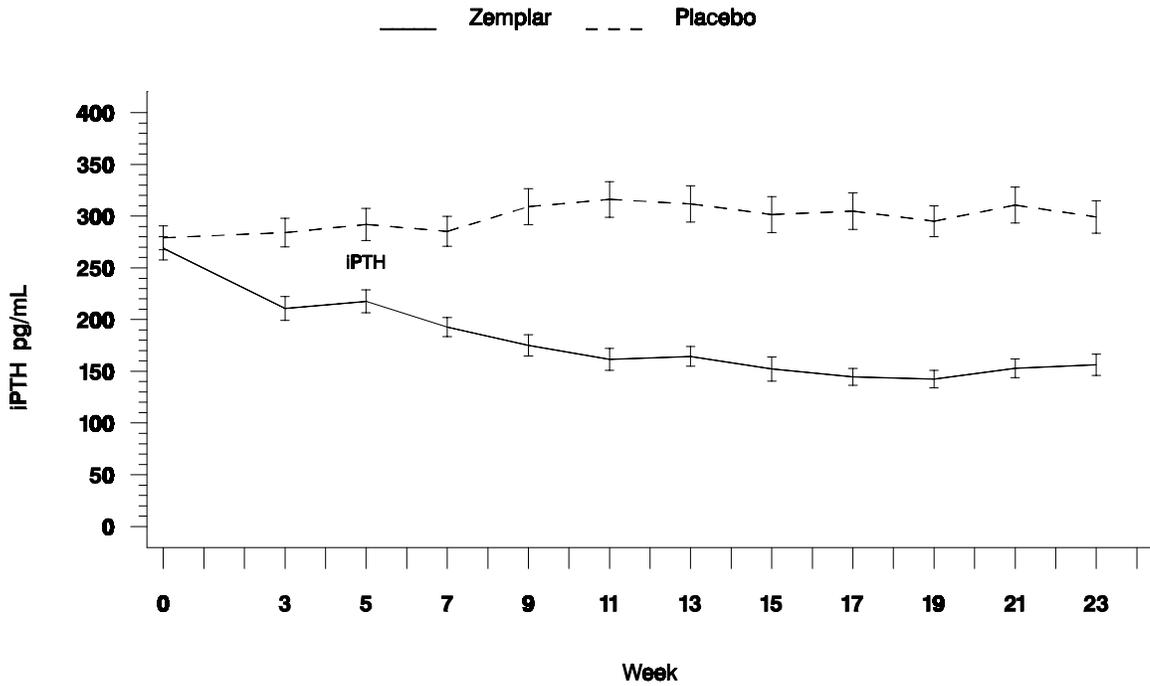
199
200 The pattern of change in the mean values for serum iPTH during the studies are shown in
201 Figure 1.

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Figure 1. Mean Values for Serum iPTH Over Time in the Three Double-Blind, Placebo-Controlled, Phase 3, CKD Stage 3 and 4 Studies Combined



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The mean changes from baseline to final treatment visit in serum iPTH, calcium, phosphorus, calcium-phosphorus product (Ca \times P), and bone-specific alkaline phosphatase are shown in Table 2.

221 **Table 2. Mean Changes from Baseline to Final Treatment Visit in Serum**
 222 **iPTH, Bone Specific Alkaline Phosphatase, Calcium, Phosphorus,**
 223 **and Calcium x Phosphorus Product in Three Double-Blind,**
 224 **Placebo-Controlled, Phase 3, CKD Stage 3 and 4 Studies**
 225 **Combined**

| | Zemlar Capsules | Placebo |
|---|-----------------|-------------|
| iPTH (pg/mL) | n = 104 | n = 110 |
| Mean Baseline Value | 266 | 279 |
| Mean Final Treatment Value | 162 | 315 |
| Mean Change from Baseline (SE) | -104 (9.2) | +35 (9.0) |
| Bone Specific Alkaline Phosphatase (mcg/L) | n = 101 | n = 107 |
| Mean Baseline | 17.1 | 18.8 |
| Mean Final Treatment Value | 9.2 | 17.4 |
| Mean Change from Baseline (SE) | -7.9 (0.76) | -1.4 (0.74) |
| Calcium (mg/dL) | n = 104 | n = 110 |
| Mean Baseline | 9.3 | 9.4 |
| Mean Final Treatment Value | 9.5 | 9.3 |
| Mean Change from Baseline (SE) | +0.2 (0.04) | -0.1 (0.04) |
| Phosphorus (mg/dL) | n = 104 | n = 110 |
| Mean Baseline | 4.0 | 4.0 |
| Mean Final Treatment Value | 4.3 | 4.3 |
| Mean Change from Baseline (SE) | +0.3 (0.08) | +0.3 (0.08) |
| Calcium x Phosphorus Product (mg ² /dL ²) | n = 104 | n = 110 |
| Mean Baseline | 36.7 | 36.9 |
| Mean Final Treatment Value | 40.7 | 39.7 |
| Mean Change from Baseline (SE) | +4.0 (0.74) | +2.9 (0.72) |

226
 227 **INDICATIONS AND USAGE**

228 Zemlar Capsules are indicated for the prevention and treatment of secondary
 229 hyperparathyroidism associated with chronic kidney disease (CKD) Stage 3 and 4.

230
 231 **CONTRAINDICATIONS**

232 Zemlar Capsules should not be given to patients with evidence of vitamin D toxicity,
 233 hypercalcemia, or hypersensitivity to any ingredient in this product (see **WARNINGS**).

234
 235 **WARNINGS**

236 Excessive administration of vitamin D compounds, including Zemlar Capsules, can
 237 cause over suppression of PTH, hypercalcemia, hypercalciuria, hyperphosphatemia, and
 238 adynamic bone disease. Progressive hypercalcemia due to overdosage of vitamin D and

239 its metabolites may be so severe as to require emergency attention. Acute hypercalcemia
240 may exacerbate tendencies for cardiac arrhythmias and seizures and may potentiate the
241 action of digitalis. Chronic hypercalcemia can lead to generalized vascular calcification
242 and other soft-tissue calcification. High intake of calcium and phosphate concomitant
243 with vitamin D compounds may lead to similar abnormalities and patient monitoring and
244 individualized dose titration is required.

245

246 Pharmacologic doses of vitamin D and its derivatives should be withheld during Zemplar
247 treatment to avoid hypercalcemia.

248

249 **PRECAUTIONS**

250

251 **General**

252 Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be
253 applied when digitalis compounds are prescribed concomitantly with Zemplar Capsules.

254

255 **Information for Patients**

256 The patient or guardian should be informed about compliance with dosage instructions,
257 adherence to instructions about diet and phosphorus restriction, and avoidance of the use
258 of unapproved nonprescription drugs. Phosphate-binding agents may be needed to
259 control serum phosphorus levels in patients, but excessive use of aluminum containing
260 compounds should be avoided. Patients also should be informed about the symptoms of
261 elevated calcium (see **ADVERSE REACTIONS**).

262

263 **Laboratory Tests**

264 During the initial dosing or following any dose adjustment of medication, serum calcium,
265 serum phosphorus, and serum or plasma iPTH should be monitored at least every two
266 weeks for 3 months after initiation of Zemplar therapy or following dose-adjustments in
267 Zemplar therapy, then monthly for 3 months, and every 3 months thereafter.

268

269 **Drug Interactions**

270 Paricalcitol is not expected to inhibit the clearance of drugs metabolized by cytochrome
271 P450 enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6
272 CYP2E1 or CYP3A nor induce the clearance of drugs metabolized by CYP2B6, CYP2C9
273 or CYP3A.

274

275 A multiple dose drug-drug interaction study demonstrated that ketoconazole
276 approximately doubled paricalcitol $AUC_{0-\infty}$ (see **CLINICAL PHARMACOLOGY**).

277 Since paricalcitol is partially metabolized by CYP3A and ketoconazole is known to be a
278 strong inhibitor of cytochrome P450 3A enzyme, care should be taken while dosing
279 paricalcitol with ketoconazole and other strong P450 3A inhibitors including atazanavir,
280 clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir,
281 telithromycin or voriconazole. Dose adjustment of Zemplar Capsules may be required,
282 and iPTH and serum calcium concentrations should be closely monitored if a patient
283 initiates or discontinues therapy with a strong CYP3A4 inhibitor such as ketoconazole.
284

285 Drugs that impair intestinal absorption of fat-soluble vitamins, such as cholestyramine,
286 may interfere with the absorption of Zemplar Capsules.

287

288 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

289 In a 104-week carcinogenicity study in CD-1 mice, an increased incidence of uterine
290 leiomyoma and leiomyosarcoma was observed at subcutaneous doses of 1, 3, 10 mcg/kg
291 given three times weekly (2 to 15 times the AUC at a human dose of 14 mcg, equivalent
292 to 0.24 mcg/kg based on AUC). The incidence rate of uterine leiomyoma was
293 significantly different than the control group at the highest dose of 10 mcg/kg. In a 104-
294 week carcinogenicity study in rats, there was an increased incidence of benign adrenal
295 pheochromocytoma at subcutaneous doses of 0.15, 0.5, 1.5 mcg/kg (< 1 to 7 times the
296 exposure following a human dose of 14 mcg, equivalent to 0.24 mcg/kg based on AUC).
297 The increased incidence of pheochromocytomas in rats may be related to the alteration of
298 calcium homeostasis by paricalcitol. Paricalcitol did not exhibit genetic toxicity *in vitro*
299 with or without metabolic activation in the microbial mutagenesis assay (Ames Assay),
300 mouse lymphoma mutagenesis assay (L5178Y), or a human lymphocyte cell
301 chromosomal aberration assay. There was also no evidence of genetic toxicity in an *in*
302 *vivo* mouse micronucleus assay. Paricalcitol had no effect on fertility (male or female) in
303 rats at intravenous doses up to 20 mcg/kg/dose (equivalent to 13 times a human dose of
304 14 mcg based on surface area, mcg/m²).

305 **Pregnancy**

306 *Pregnancy category C*

307

308 Paricalcitol has been shown to cause minimal decreases in fetal viability (5%) when
309 administered daily to rabbits at a dose 0.5 times a human dose of 14 mcg or 0.24 mcg/kg
310 (based on body surface area, mcg/m²), and when administered to rats at a dose two times
311 the 0.24 mcg/kg human dose (based on body surface area, mcg/m²). At the highest dose
312 tested, 20 mcg/kg administered three times per week in rats (13 times the 14 mcg human
313 dose based on surface area, mcg/m²), there was a significant increase in the mortality of
314 newborn rats at doses that were maternally toxic and are known to produce
315 hypercalcemia in rats. No other effects on offspring development were observed.
316 Paricalcitol was not teratogenic at the doses tested.

317

318 Paricalcitol (20 mcg/kg) has been shown to cross the placental barrier in rats.
319 There are no adequate and well-controlled clinical studies in pregnant women. Zemplar
320 Capsules should be used during pregnancy only if the potential benefit to the mother
321 justifies the potential risk to the fetus.

322

323 **Nursing Mothers**

324 Studies in rats have shown that paricalcitol is present in the milk. It is not known whether
325 paricalcitol is excreted in human milk. In the nursing patient, a decision should be made
326 whether to discontinue nursing or to discontinue the drug, taking into account the
327 importance of the drug to the mother.

328

329 **Geriatric Use**

330 Of the total number (n = 220) of patients in clinical studies of Zemplar Capsules, 49%
331 were 65 and over, while 17% were 75 and over. No overall differences in safety and
332 effectiveness were observed between these patients and younger patients, and other
333 reported clinical experience has not identified differences in responses between the
334 elderly and younger patients, but greater sensitivity of some older individuals cannot be
335 ruled out.

336

337 **Pediatric Use**

338 Safety and efficacy of Zemplar Capsules in pediatric patients have not been established.

339

340 **ADVERSE REACTIONS**

341 The safety of Zemplar Capsules has been evaluated in three 24-week (approximately six-
 342 month), double-blind, placebo-controlled, multicenter clinical studies involving 220 CKD
 343 Stage 3 and 4 patients. Six percent (6%) of Zemplar Capsules treated patients and 4% of
 344 placebo treated patients discontinued from clinical studies due to an adverse event. All
 345 reported adverse events occurring in at least 2% in either treatment group are presented in
 346 Table 3.

347
 348 **Table 3. Treatment - Emergent Adverse Events by Body System Occurring**
 349 **in 2% of Subjects in the Zemplar-Treated Group of Three,**
 350 **Double-Blind, Placebo-Controlled, Phase 3, CKD Stage 3 and 4**
 351 **Studies; All Treated Patients**

| Body System ^a COSTART V Term | Number (%) of Subjects | | | |
|--|-------------------------------|--------------|----------------------|--------------|
| | Zemplar Capsules (n = 107) | | Placebo (n = 113) | |
| Overall | 88 | (82%) | 86 | (76%) |
| Body as a Whole | 49 | (46%) | 40 | (35%) |
| Accidental Injury | 10 | (9%) | 8 | (7%) |
| Pain | 8 | (7%) | 7 | (6%) |
| Viral Infection | 8 | (7%) | 8 | (7%) |
| Allergic Reaction | 6 | (6%) | 2 | (2%) |
| Headache | 5 | (5%) | 5 | (4%) |
| Abdominal Pain | 4 | (4%) | 2 | (2%) |
| Back Pain | 4 | (4%) | 1 | (1%) |
| Infection | 4 | (4%) | 4 | (4%) |
| Asthena | 3 | (3%) | 2 | (2%) |
| Chest Pain | 3 | (3%) | 1 | (1%) |
| Fever | 3 | (3%) | 1 | (1%) |
| Infection Fungal | 3 | (3%) | 0 | (0%) |
| Cyst | 2 | (2%) | 0 | (0%) |
| Flu Syndrome | 2 | (2%) | 1 | (1%) |
| Infection Bacterial | 2 | (2%) | 1 | (1%) |
| Cardiovascular | 27 | (25%) | 19 | (17%) |
| Hypertension | 7 | (7%) | 4 | (4%) |
| Hypotension | 5 | (5%) | 3 | (3%) |
| Syncope | 3 | (3%) | 1 | (1%) |
| Cardiomyopathy | 2 | (2%) | 0 | (0%) |
| Congestive Heart Failure | 2 | (2%) | 5 | (4%) |
| Myocardial Infarct | 2 | (2%) | 0 | (0%) |
| Postural Hypotension | 2 | (2%) | 0 | (0%) |
| Digestive | 29 | (27%) | 31 | (27%) |
| Diarrhea | 7 | (7%) | 5 | (4%) |
| Nausea | 6 | (6%) | 4 | (4%) |
| Vomiting | 6 | (6%) | 5 | (4%) |
| Constipation | 4 | (4%) | 4 | (4%) |

| | | | | |
|--|-----------|--------------|-----------|--------------|
| Gastroenteritis | 3 | (3%) | 3 | (3%) |
| Dyspepsia | 2 | (2%) | 2 | (2%) |
| Gastritis | 2 | (2%) | 4 | (4%) |
| Rectal Disorder | 2 | (2%) | 0 | (0%) |
| Hemic and Lymphatic System | 4 | (4%) | 10 | (9%) |
| Hypervolemia | 2 | (2%) | 4 | (4%) |
| Ecchymosis | 2 | (2%) | 4 | (4%) |
| Metabolic and Nutritional Disorders | 24 | (22%) | 34 | (30%) |
| Edema | 7 | (7%) | 5 | (4%) |
| Uremia | 7 | (7%) | 9 | (8%) |
| Gout | 4 | (4%) | 6 | (5%) |
| Dehydration | 3 | (3%) | 1 | (1%) |
| Acidosis | 2 | (2%) | 1 | (1%) |
| Hyperkalemia | 2 | (2%) | 3 | (3%) |
| Hyperphosphatemia | 2 | (2%) | 4 | (4%) |
| Hypoglycemia | 2 | (2%) | 4 | (4%) |
| Hypokalemia | 2 | (2%) | 1 | (1%) |
| Musculoskeletal | 12 | (11%) | 9 | (8%) |
| Arthritis | 5 | (5%) | 1 | (1%) |
| Leg Cramps | 3 | (3%) | 0 | (0%) |
| Myalgia | 2 | (2%) | 5 | (4%) |
| Nervous | 18 | (17%) | 12 | (11%) |
| Dizziness | 5 | (5%) | 5 | (4%) |
| Vertigo | 5 | (5%) | 0 | (0%) |
| Depression | 3 | (3%) | 0 | (0%) |
| Insomnia | 2 | (2%) | 2 | (2%) |
| Neuropathy | 2 | (2%) | 1 | (1%) |
| Respiratory | 26 | (24%) | 25 | (22%) |
| Pharyngitis | 11 | (10%) | 12 | (11%) |
| Rhinitis | 5 | (5%) | 4 | (4%) |
| Bronchitis | 3 | (3%) | 1 | (1%) |
| Cough Increased | 3 | (3%) | 2 | (2%) |
| Sinusitis | 3 | (3%) | 1 | (1%) |
| Epistaxis | 2 | (2%) | 1 | (1%) |
| Pneumonia | 2 | (2%) | 0 | (0%) |
| Skin and Appendages | 17 | (16%) | 10 | (9%) |
| Rash | 6 | (6%) | 3 | (3%) |
| Pruritus | 3 | (3%) | 3 | (3%) |
| Skin Ulcer | 3 | (3%) | 0 | (0%) |
| Skin Hypertrophy | 2 | (2%) | 0 | (0%) |
| Vesiculobullous Rash | 2 | (2%) | 1 | (1%) |
| Special Senses | 9 | (8%) | 11 | (10%) |
| Amblyopia | 2 | (2%) | 0 | (0%) |
| Retinal Disorder | 2 | (2%) | 0 | (0%) |
| Urogenital System | 10 | (9%) | 10 | (9%) |
| Urinary Tract Infection | 3 | (3%) | 1 | (1%) |
| Kidney Function Abnormal | 2 | (2%) | 1 | (1%) |

352 a. Includes all patients with events in that body system.

353

354

355 Potential adverse effects of Zemplar Capsules are, in general, similar to those
356 encountered with excessive vitamin D intake. The early and late signs and symptoms of
357 hypercalcemia associated with vitamin D overdoses include:

358
359 *Early:* Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation,
360 muscle pain, bone pain, and metallic taste.

361
362 *Late:* Anorexia, weight loss, conjunctivitis (calcific), pancreatitis, photophobia,
363 rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN,
364 hypercholesterolemia, elevated AST and ALT, ectopic calcification, hypertension,
365 cardiac arrhythmias, somnolence, death, and, rarely, overt psychosis.

366
367

OVERDOSAGE

368 Excessive administration of Zemplar Capsules can cause hypercalcemia, hypercalciuria,
369 and hyperphosphatemia, and over suppression of PTH. (See **WARNINGS**.)

370
371

Treatment of Overdosage

372 The treatment of acute overdosage of Zemplar Capsules should consist of general
373 supportive measures. If drug ingestion is discovered within a relatively short time,
374 induction of emesis or gastric lavage may be of benefit in preventing further absorption.
375 If the drug has passed through the stomach, the administration of mineral oil may
376 promote its fecal elimination. Serial serum electrolyte determinations (especially
377 calcium), rate of urinary calcium excretion, and assessment of electrocardiographic
378 abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in
379 patients receiving digitalis. Discontinuation of supplemental calcium and institution of a
380 low-calcium diet are also indicated in accidental overdosage. Due to the relatively short
381 duration of the pharmacological action of paricalcitol, further measures are probably
382 unnecessary. If persistent and markedly elevated serum calcium levels occur, there are a
383 variety of therapeutic alternatives that may be considered depending on the patient's
384 underlying condition. These include the use of drugs such as phosphates and
385 corticosteroids, as well as measures to induce an appropriate forced diuresis.

386
387

DOSAGE AND ADMINISTRATION

388 Zemplar Capsules may be administered daily or three times a week. When dosing three
389 times weekly, the dose should be administered no more frequently than every other day.
390 The average weekly doses for both daily and three times a week dosage regimens are
391 similar (See **CLINICAL STUDIES**).

392

393 Zemplar Capsules may be taken without regard to food. No dosing adjustment is
 394 required in patients with mild and moderate hepatic impairment.

395
 396 **Initial Dose**

397 The initial dose of Zemplar Capsules is based on baseline intact parathyroid hormone
 398 (iPTH) levels.

399

| Baseline iPTH Level | Daily Dose | Three Times a Week Dose* |
|---------------------|------------|--------------------------|
| ≤ 500 pg/mL | 1 mcg | 2 mcg |
| > 500 pg/mL | 2 mcg | 4 mcg |

* To be administered not more often than every other day

400

401 **Dose Titration**

402

403 Dosing must be individualized and based on serum or plasma iPTH levels, with
 404 monitoring of serum calcium and serum phosphorus. The following is a suggested
 405 approach in titration.

406

| iPTH Level Relative to Baseline | Zemplar Capsule Dose | Dose Adjustment at 2 to 4 Week Intervals | |
|---------------------------------|----------------------|--|----------------------------|
| | | Daily Dosage | Three Times a Week Dosage* |
| The same or increased | Increase | 1 mcg | 2 mcg |
| Decreased by < 30% | | | |
| Decreased by ≥30%, ≤60% | Maintain | | |
| Decreased > 60% | Decrease | 1 mcg | 2 mcg |
| iPTH < 60 pg/mL | | | |

407

* To be administered not more often than every other day

408

409 If a patient is taking the lowest dose on the daily regimen and a dose reduction is needed,
 410 the dose can be decreased to 1 mcg three times a week. If a further dose reduction is
 411 required, the drug should be withheld as needed and can be restarted at a lower dose. If a
 412 patient is on a calcium-based phosphate binder, the binder dose may be decreased or
 413 withheld, or the patient may be switched to a non-calcium-based phosphate binder. If
 414 hypercalcemia or an elevated Ca×P is observed, the dose of Zemplar should be reduced
 415 or interrupted until these parameters are normalized.

416

417 Serum calcium and phosphorus levels should be closely monitored after initiation of
418 Zemplar Capsules and during dose titration periods and coadministration with strong
419 P450 3A inhibitors (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).
420

421 **HOW SUPPLIED**

422 Zemplar Capsules are available as 1 mcg, 2 mcg, and 4 mcg capsules.

423 The 1 mcg capsule is an oval, gray, soft gelatin capsule imprinted with  and ZA, and is
424 available in the following package size:

425
426 Bottles of 30 (NDC 0074-4317-30)
427

428 The 2 mcg capsule is an oval, orange-brown, soft gelatin capsule imprinted with  and
429 ZF, and is available in the following package size:

430
431 Bottles of 30 (NDC 0074-4314-30)
432

433 The 4 mcg capsule is an oval, gold soft gelatin capsule imprinted with  and ZK, and is
434 available in the following package size:

435
436 Bottles of 30 (NDC 0074-4315-30)
437

438 **Storage**

439 Store Zemplar Capsules at 25°C (77°F). Excursions permitted between 15°- 30°C (59°-
440 86°F). See USP Controlled Room Temperature.

441
442 U.S. patents: 5,246,925; 5,587,497
443

444 **REFERENCES**

- 445 1. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in
446 Chronic Kidney Disease. Am J Kidney Dis 2003; Volume 42(4): Supplement 3.

447
448 NEW

449
450 Revised: NEW

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PRINTED IN U.S.A.

451
452

Exp.

Lot

02-8986-2/R1

Store at
25°C (77°F)
(see insert).



30 Capsules

Rx only



Abbott

NDC 0074-4317-30

Zemplar[®] (paricalcitol) Capsules

1 mcg

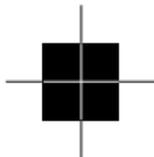
Dispense in a USP tight container. Do not accept if seal over bottle opening is broken or missing.

Each capsule contains:
1 mcg Paricalcitol, USP
See package insert for full prescribing information.

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North Chicago, IL 60064, USA



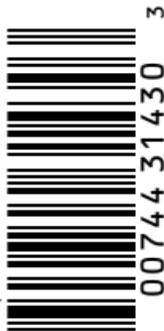


Exp.

Lot

02-8987-2/R1

Store at
25°C (77°F)
(see insert).



30 Capsules

Rx only



Zemplar[®] (paricalcitol) Capsules

2 mcg

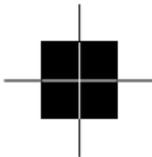
NDC 0074-4314-30

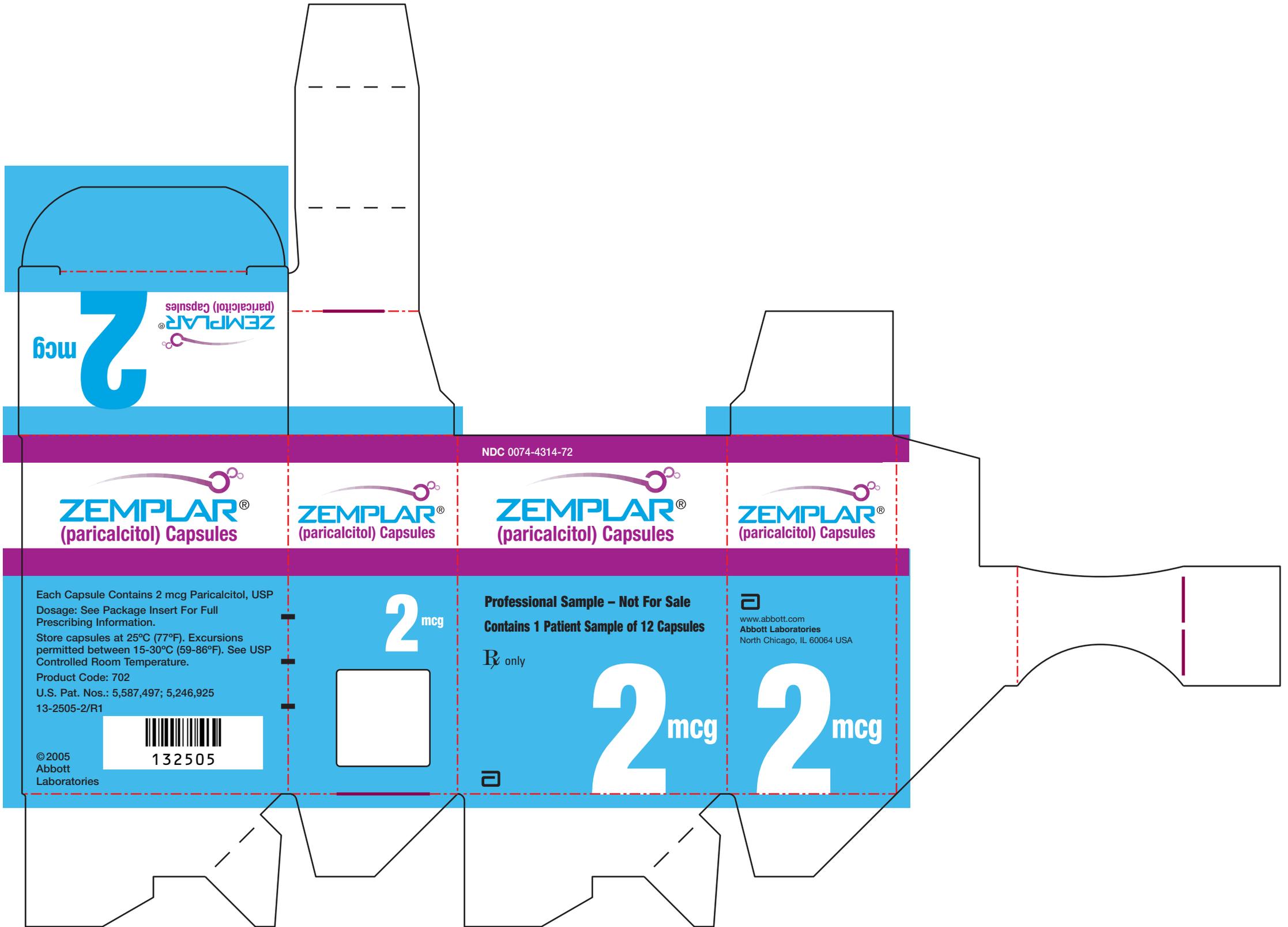
Dispense in a USP tight container. Do not accept if seal over bottle opening is broken or missing.

Each capsule contains:
2 mcg Paricalcitol, USP
See package insert for full prescribing information.

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2 mcg
ZEMPLAR[®]
(paricalcitol) Capsules

NDC 0074-4314-72

ZEMPLAR[®]
(paricalcitol) Capsules

ZEMPLAR[®]
(paricalcitol) Capsules

ZEMPLAR[®]
(paricalcitol) Capsules

ZEMPLAR[®]
(paricalcitol) Capsules

Each Capsule Contains 2 mcg Paricalcitol, USP
Dosage: See Package Insert For Full
Prescribing Information.

Store capsules at 25°C (77°F). Excursions
permitted between 15-30°C (59-86°F). See USP
Controlled Room Temperature.

Product Code: 702

U.S. Pat. Nos.: 5,587,497; 5,246,925

13-2505-2/R1



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Laboratories

2 mcg

Professional Sample - Not For Sale
Contains 1 Patient Sample of 12 Capsules

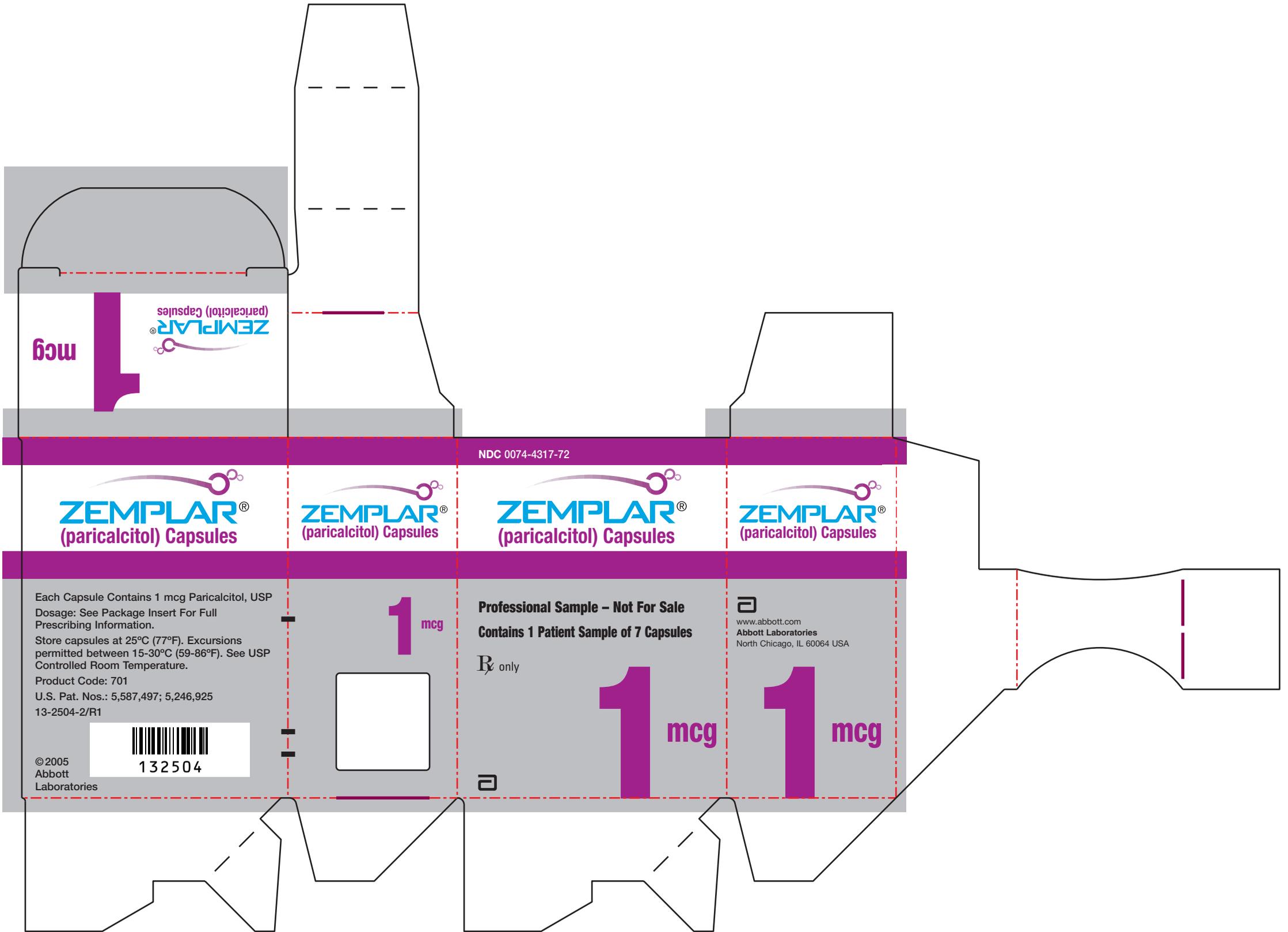
R_x only


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2 mcg

2 mcg





mcg

ZEMPLAR[®]
(paricalcitol) Capsules

NDC 0074-4317-72

ZEMPLAR[®]
(paricalcitol) Capsules

ZEMPLAR[®]
(paricalcitol) Capsules

ZEMPLAR[®]
(paricalcitol) Capsules

ZEMPLAR[®]
(paricalcitol) Capsules

Each Capsule Contains 1 mcg Paricalcitol, USP
Dosage: See Package Insert For Full
Prescribing Information.

Store capsules at 25°C (77°F). Excursions
permitted between 15-30°C (59-86°F). See USP
Controlled Room Temperature.

Product Code: 701

U.S. Pat. Nos.: 5,587,497; 5,246,925

13-2504-2/R1



132504

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1 mcg

Professional Sample – Not For Sale
Contains 1 Patient Sample of 7 Capsules

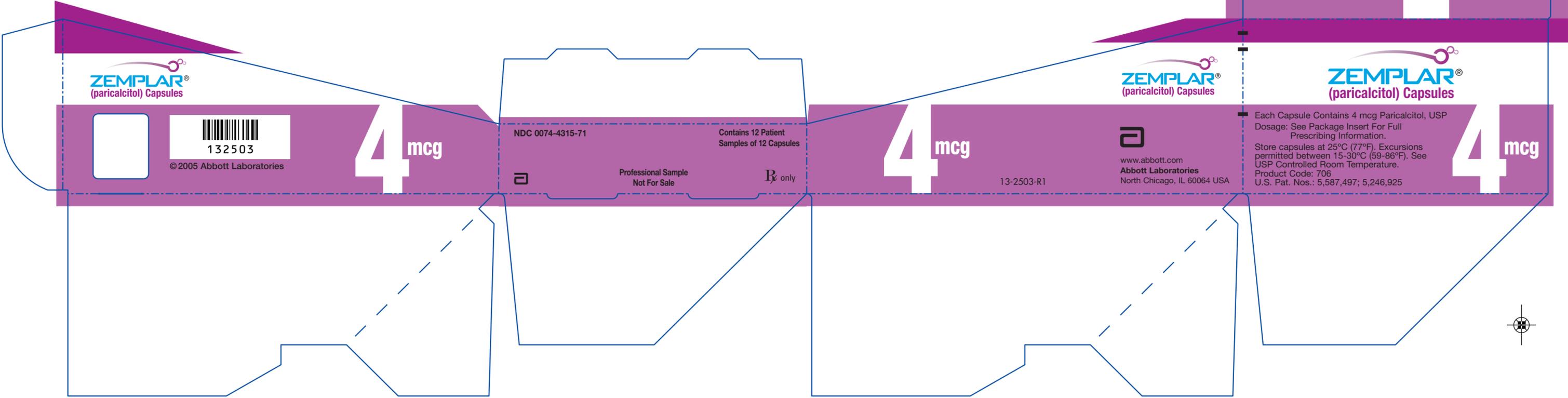
Rx only


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1 mcg

1 mcg





ZEMPLAR[®]
(paricalcitol) Capsules



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4 mcg

NDC 0074-4315-71



Professional Sample
Not For Sale

Contains 12 Patient
Samples of 12 Capsules

R_x only

4 mcg

13-2503-R1

ZEMPLAR[®]
(paricalcitol) Capsules

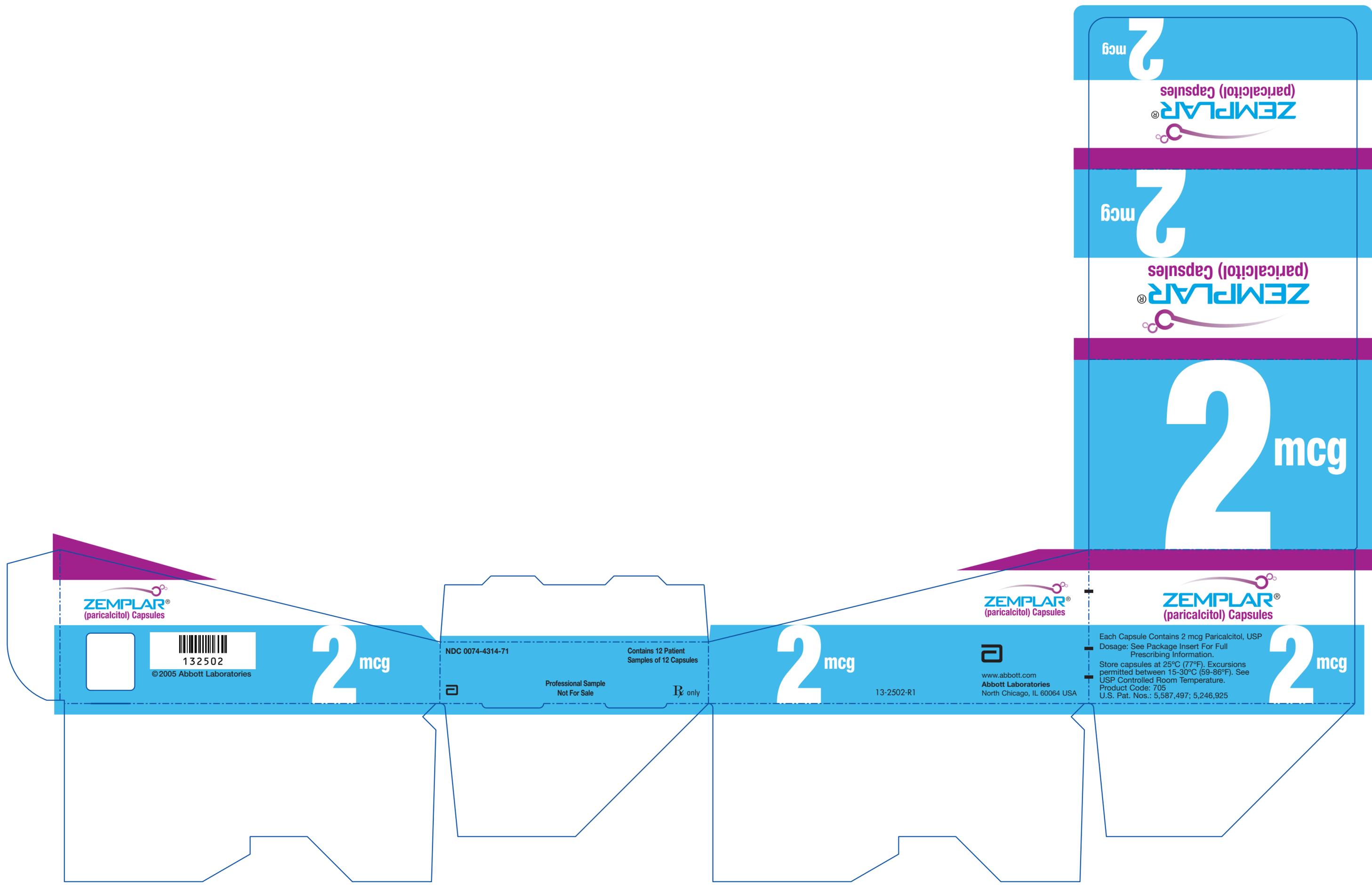


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ZEMPLAR[®]
(paricalcitol) Capsules

Each Capsule Contains 4 mcg Paricalcitol, USP
Dosage: See Package Insert For Full
Prescribing Information.
Store capsules at 25°C (77°F). Excursions
permitted between 15-30°C (59-86°F). See
USP Controlled Room Temperature.
Product Code: 706
U.S. Pat. Nos.: 5,587,497; 5,246,925

4 mcg



ZEMPLAR[®]
(paricalcitol) Capsules



132502
© 2005 Abbott Laboratories

2 mcg

NDC 0074-4314-71

Contains 12 Patient
Samples of 12 Capsules



Professional Sample
Not For Sale

Rx only

2 mcg

13-2502-R1



ZEMPLAR[®]
(paricalcitol) Capsules

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Each Capsule Contains 2 mcg Paricalcitol, USP
Dosage: See Package Insert For Full
Prescribing Information.
Store capsules at 25°C (77°F). Excursions
permitted between 15-30°C (59-86°F). See
USP Controlled Room Temperature.
Product Code: 705
U.S. Pat. Nos.: 5,587,497; 5,246,925

2 mcg

2 mcg

ZEMPLAR[®]
(paricalcitol) Capsules

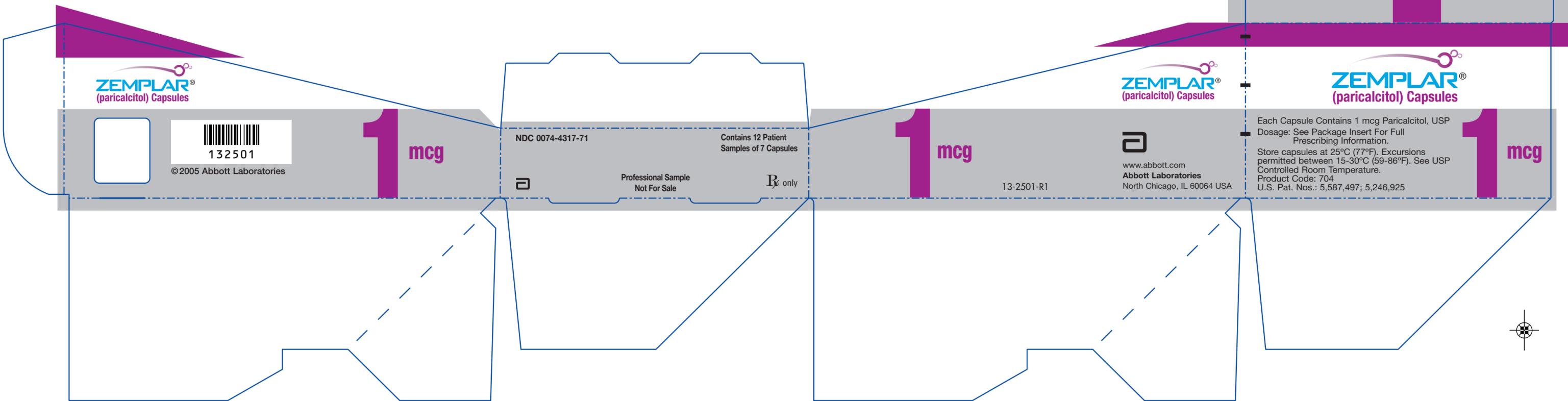
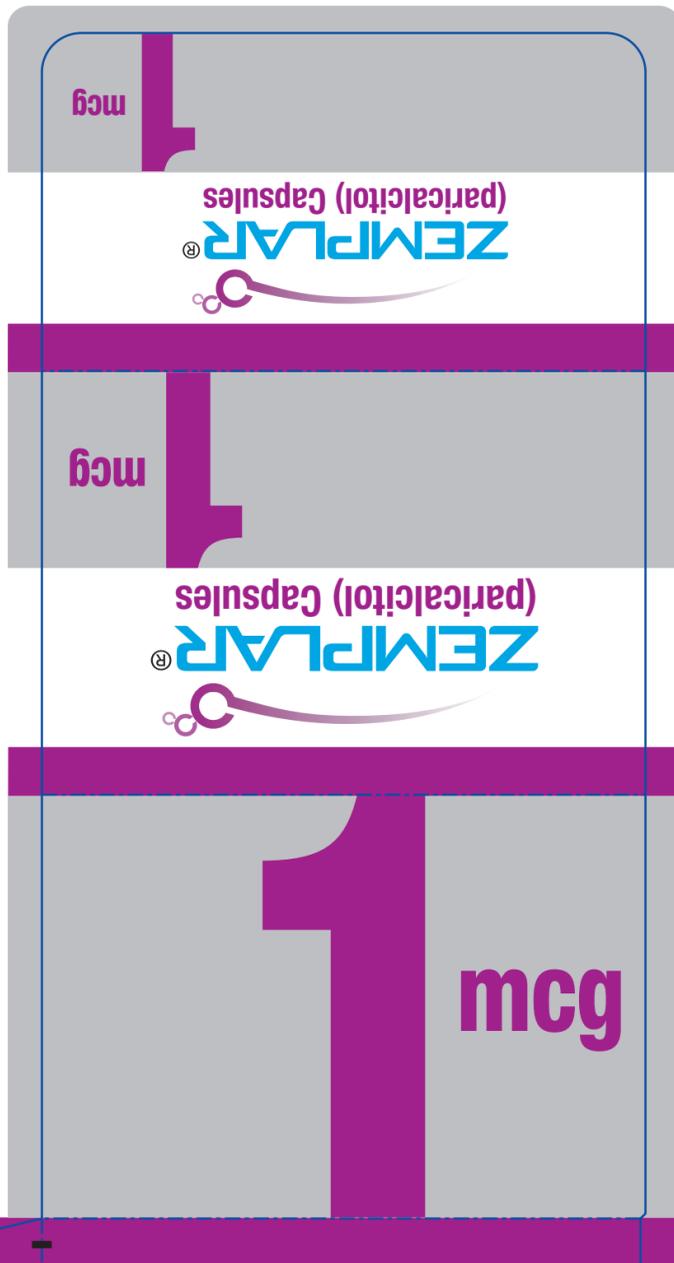
2 mcg

ZEMPLAR[®]
(paricalcitol) Capsules

2 mcg

ZEMPLAR[®]
(paricalcitol) Capsules





ZEMPLAR[®]
(paricalcitol) Capsules



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1 mcg

NDC 0074-4317-71



Professional Sample
Not For Sale

Contains 12 Patient
Samples of 7 Capsules

R_x only

1 mcg

13-2501-R1

ZEMPLAR[®]
(paricalcitol) Capsules

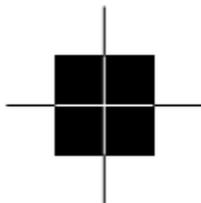


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ZEMPLAR[®]
(paricalcitol) Capsules

Each Capsule Contains 1 mcg Paricalcitol, USP
Dosage: See Package Insert For Full
Prescribing Information.
Store capsules at 25°C (77°F). Excursions
permitted between 15-30°C (59-86°F). See USP
Controlled Room Temperature.
Product Code: 704
U.S. Pat. Nos.: 5,587,497; 5,246,925

1 mcg



Exp.

Lot
02-9149-2/R1

NDC 0074-4315-71 12 Capsules

Zemplar[®]
(paricalcitol) Capsules

4 mcg

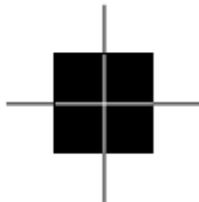
Professional Sample – Not for Sale

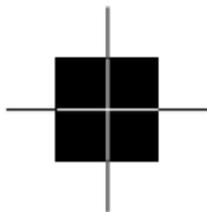
Rx only



Do not accept if seal over
bottle opening is broken or
missing. Store at 25°C
(77°F) (see insert).

Each capsule contains:
4 mcg Paricalcitol, USP
See package insert for full
prescribing information.
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Exp.

Lot
02-9148-2/R1

NDC 0074-4314-71 12 Capsules

Zemplar[®]
(paricalcitol) Capsules

2 mcg

Professional Sample – Not for Sale

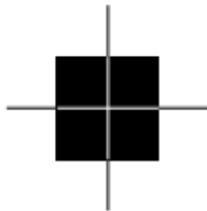
Rx only

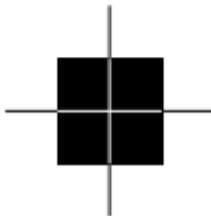


Do not accept if seal over
bottle opening is broken or
missing. Store at 25°C
(77°F) (see insert).

Each capsule contains:
2 mcg Paricalcitol, USP
See package insert for full
prescribing information.

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Exp.

Lot
02-9147-2/R1

NDC 0074-4317-71 7 Capsules

Zemplar[®]
(paricalcitol) Capsules

1 mcg

Professional Sample – Not for Sale

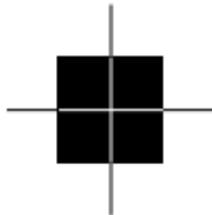
Rx only

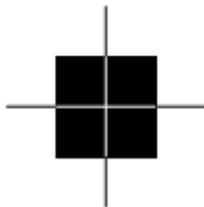


Do not accept if seal over
bottle opening is broken or
missing. Store at 25°C
(77°F) (see insert).

Each capsule contains:
1 mcg Paricalcitol, USP
See package insert for full
prescribing information.

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Exp.

Lot
02-8991-2/R1

NDC 0074-4315-72 12 Capsules

Zemplar[®]
(paricalcitol) Capsules

4 mcg

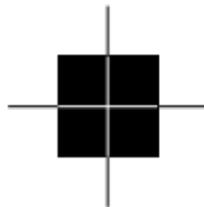
Professional Sample – Not for Sale

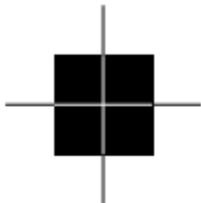
Rx only



Do not accept if seal over
bottle opening is broken or
missing. Store at 25°C
(77°F) (see insert).

Each capsule contains:
4 mcg Paricalcitol, USP
See package insert for full
prescribing information.
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N. Chicago, IL 60064, USA





Exp.

Lot
02-8990-2/R1

NDC 0074-4314-72 12 Capsules

Zemplar[®]
(paricalcitol) Capsules

2 mcg

Professional Sample – Not for Sale

Rx only



Do not accept if seal over
bottle opening is broken or
missing. Store at 25°C

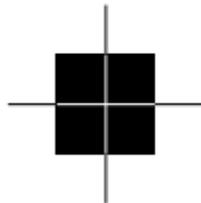
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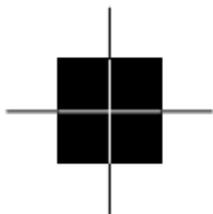
Each capsule contains:

2 mcg Paricalcitol, USP

See package insert for full
prescribing information.

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Exp.

Lot
02-8989-2/R1

NDC 0074-4317-72 7 Capsules

Zemplar[®]
(paricalcitol) Capsules

1 mcg

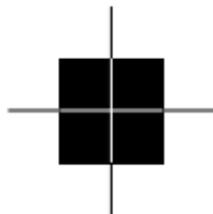
Professional Sample – Not for Sale

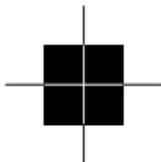
Rx only



Do not accept if seal over
bottle opening is broken or
missing. Store at 25°C
(77°F) (see insert).

Each capsule contains:
1 mcg Paricalcitol, USP
See package insert for full
prescribing information.
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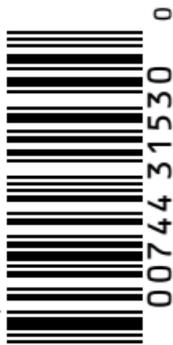


Exp.

Store at
25°C (77°F)
(see insert).

Lot

02-8988-2/R1



3

30 Capsules

Rx only



Abbott

NDC 0074-4315-30

Zemplar[®] (paricalcitol) Capsules

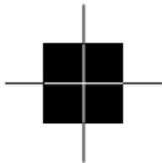
4 mcg

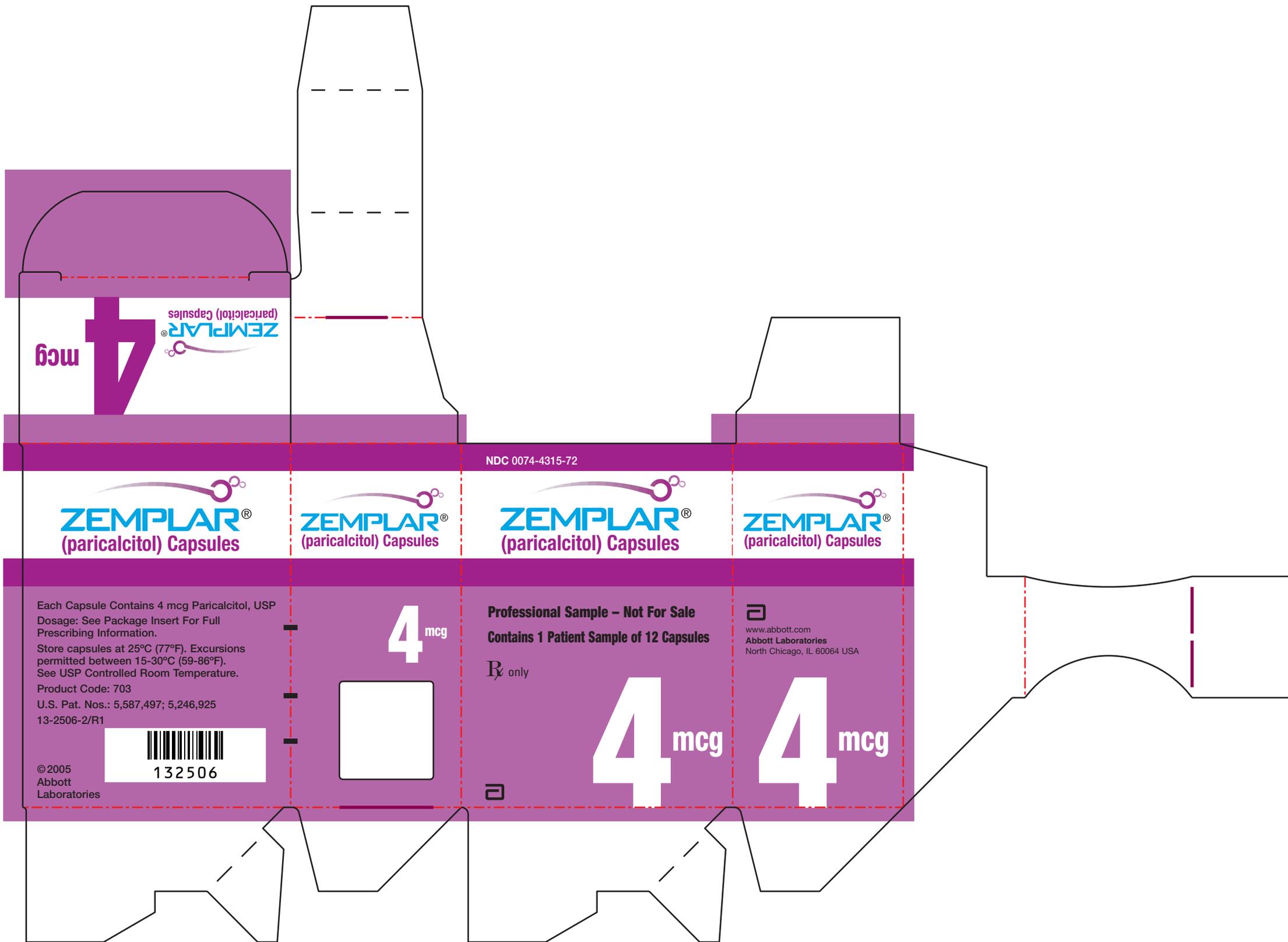
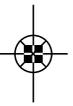
Dispense in a USP tight container. Do not accept if seal over bottle opening is broken or missing.

Each capsule contains: 4 mcg Paricalcitol, USP
See package insert for full prescribing information.

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4 mcg
ZEMPLAR[®]
(paricalcitol) Capsules

NDC 0074-4315-72

ZEMPLAR[®]
(paricalcitol) Capsules

ZEMPLAR[®]
(paricalcitol) Capsules

ZEMPLAR[®]
(paricalcitol) Capsules

ZEMPLAR[®]
(paricalcitol) Capsules

Each Capsule Contains 4 mcg Paricalcitol, USP
Dosage: See Package Insert For Full
Prescribing Information.
Store capsules at 25°C (77°F). Excursions
permitted between 15-30°C (59-86°F).
See USP Controlled Room Temperature.
Product Code: 703
U.S. Pat. Nos.: 5,587,497; 5,246,925
13-2506-2/R1

4 mcg

Professional Sample - Not For Sale
Contains 1 Patient Sample of 12 Capsules


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Rx only

4 mcg

4 mcg



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