



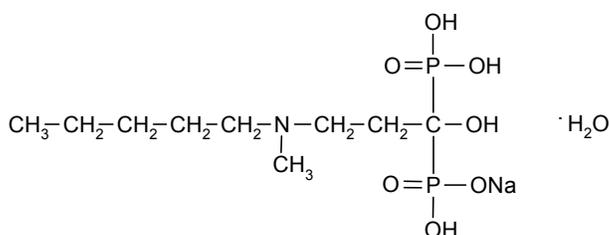
BONIVA[®]
(ibandronate sodium)
TABLETS

1
2
3
4
5

6 **R_x only**

7 **DESCRIPTION**

8 BONIVA (ibandronate sodium) is a nitrogen-containing bisphosphonate that inhibits
 9 osteoclast-mediated bone resorption. The chemical name for ibandronate sodium is 3-(*N*-
 10 methyl-*N*-pentyl) amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt,
 11 monohydrate with the molecular formula C₉H₂₂NO₇P₂Na·H₂O and a molecular weight of
 12 359.24. Ibandronate sodium is a white- to off-white powder. It is freely soluble in water
 13 and practically insoluble in organic solvents. Ibandronate sodium has the following
 14 structural formula:



15

16 BONIVA is available as a white, oblong, 2.5-mg film-coated tablet for daily oral
 17 administration or as a white, oblong, 150-mg film-coated tablet for once-monthly oral
 18 administration. One 2.5-mg film-coated tablet contains 2.813 mg ibandronate
 19 monosodium monohydrate, equivalent to 2.5 mg free acid. One 150-mg film-coated
 20 tablet contains 168.75 mg ibandronate monosodium monohydrate, equivalent to 150 mg
 21 free acid. BONIVA also contains the following inactive ingredients: lactose
 22 monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid,
 23 colloidal silicon dioxide, and purified water. The tablet film coating contains
 24 hypromellose, titanium dioxide, talc, polyethylene glycol 6000, and purified water.

25 **CLINICAL PHARMACOLOGY**

26 **Mechanism of Action**

27 The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which
 28 is part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces
 29 bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of
 30 bone turnover, leading to, on average, a net gain in bone mass.

31 **Pharmacokinetics**

32 **Absorption**

33 The absorption of oral ibandronate occurs in the upper gastrointestinal tract. Plasma
34 concentrations increase in a dose-linear manner up to 50 mg oral intake and increases
35 nonlinearly above this dose.

36 Following oral dosing, the time to maximum observed plasma ibandronate concentrations
37 ranged from 0.5 to 2 hours (median 1 hour) in fasted healthy postmenopausal women.
38 The mean oral bioavailability of 2.5 mg ibandronate was about 0.6% compared to
39 intravenous dosing. The extent of absorption is impaired by food or beverages (other than
40 plain water). The oral bioavailability of ibandronate is reduced by about 90% when
41 BONIVA is administered concomitantly with a standard breakfast in comparison with
42 bioavailability observed in fasted subjects. There is no meaningful reduction in
43 bioavailability when ibandronate is taken at least 60 minutes before a meal. However,
44 both bioavailability and the effect on bone mineral density (BMD) are reduced when food
45 or beverages are taken less than 60 minutes following an ibandronate dose.

46 **Distribution**

47 After absorption, ibandronate either rapidly binds to bone or is excreted into urine. In
48 humans, the apparent terminal volume of distribution is at least 90 L, and the amount of
49 dose removed from the circulation via the bone is estimated to be 40% to 50% of the
50 circulating dose. In vitro protein binding in human serum was 99.5% to 90.9% over an
51 ibandronate concentration range of 2 to 10 ng/mL in one study and approximately 85.7%
52 over a concentration range of 0.5 to 10 ng/mL in another study.

53 **Metabolism**

54 There is no evidence that ibandronate is metabolized in humans.

55 **Elimination**

56 The portion of ibandronate that is not removed from the circulation via bone absorption is
57 eliminated unchanged by the kidney (approximately 50% to 60% of the absorbed dose).
58 Unabsorbed ibandronate is eliminated unchanged in the feces.

59 The plasma elimination of ibandronate is multiphasic. Its renal clearance and distribution
60 into bone accounts for a rapid and early decline in plasma concentrations, reaching 10%
61 of the C_{max} within 3 or 8 hours after intravenous or oral administration, respectively. This
62 is followed by a slower clearance phase as ibandronate redistributes back into the blood
63 from bone. The observed apparent terminal half-life for ibandronate is generally
64 dependent on the dose studied and on assay sensitivity. The observed apparent terminal
65 half-life for the 150 mg ibandronate tablet upon oral administration to healthy
66 postmenopausal women ranges from 37 to 157 hours.

67 Total clearance of ibandronate is low, with average values in the range 84 to
68 160 mL/min. Renal clearance (about 60 mL/min in healthy postmenopausal females)
69 accounts for 50% to 60% of total clearance and is related to creatinine clearance. The

70 difference between the apparent total and renal clearances likely reflects bone uptake of
71 the drug.

72 **Special Populations**

73 **Pediatrics**

74 The pharmacokinetics of ibandronate has not been studied in patients <18 years of age.

75 **Gender**

76 The bioavailability and pharmacokinetics of ibandronate are similar in both men and
77 women.

78 **Geriatric**

79 Since ibandronate is not known to be metabolized, the only difference in ibandronate
80 elimination for geriatric patients versus younger patients is expected to relate to
81 progressive age-related changes in renal function (see **Special Populations: Renal**
82 **Impairment**).

83 **Race**

84 Pharmacokinetic differences due to race have not been studied.

85 **Renal Impairment**

86 Renal clearance of ibandronate in patients with various degrees of renal impairment is
87 linearly related to creatinine clearance (CL_{cr}).

88 Following a single dose of 0.5 mg ibandronate by intravenous administration, patients
89 with CL_{cr} 40 to 70 mL/min had 55% higher exposure (AUC_∞) than the exposure
90 observed in subjects with CL_{cr} >90 mL/min. Patients with CL_{cr} <30 mL/min had more
91 than a two-fold increase in exposure compared to the exposure for healthy subjects (see
92 **DOSAGE AND ADMINISTRATION: Patients with Renal Impairment**).

93 **Hepatic Impairment**

94 No studies have been performed to assess the pharmacokinetics of ibandronate in patients
95 with hepatic impairment since ibandronate is not metabolized in the human liver.

96 **Drug Interactions**

97 Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic
98 cytochrome P450 system. Ibandronate is eliminated by renal excretion. Based on a rat
99 study, the ibandronate secretory pathway does not appear to include known acidic or
100 basic transport systems involved in the excretion of other drugs.

101 Products containing calcium and other multivalent cations (such as aluminum,
102 magnesium, iron), including milk, food, and antacids are likely to interfere with
103 absorption of ibandronate, which is consistent with findings in animal studies.

104 H2 Blockers and Proton Pump Inhibitors (PPIs)

105 A pharmacokinetic interaction study in healthy volunteers demonstrated that 75 mg
106 ranitidine (25 mg injected intravenously 90 and 15 minutes before and 30 minutes after
107 ibandronate administration) increased the oral bioavailability of 10 mg ibandronate by
108 about 20%. This degree of increase is not considered to be clinically relevant.

109 Tamoxifen

110 A pharmacokinetic interaction study in healthy postmenopausal women demonstrated
111 that there was no interaction between oral 30 mg tamoxifen and intravenous 2 mg
112 ibandronate.

113 Pharmacodynamics

114 Osteoporosis is characterized by decreased bone mass and increased fracture risk, most
115 commonly at the spine, hip, and wrist. The diagnosis can be confirmed by a finding of
116 low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height
117 loss or kyphosis indicative of vertebral fracture. While osteoporosis occurs in both men
118 and women, it is most common among women following menopause. In healthy humans,
119 bone formation and resorption are closely linked; old bone is resorbed and replaced by
120 newly formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone
121 formation, leading to bone loss and increased risk of fracture. After menopause, the risk
122 of fractures of the spine and hip increases; approximately 40% of 50-year-old women
123 will experience an osteoporosis-related fracture during their remaining lifetimes.

124 BONIVA produced biochemical changes indicative of dose-dependent inhibition of bone
125 resorption, including decreases of biochemical markers of bone collagen degradation
126 (such as deoxypyridinoline, and cross-linked C-telopeptide of Type I collagen) in the
127 daily dose range of 0.25 to 5.0 mg and once-monthly doses from 100 mg to 150 mg in
128 postmenopausal women.

129 Treatment with 2.5 mg daily BONIVA resulted in decreases in biochemical markers of
130 bone turnover, including urinary C-terminal telopeptide of Type I collagen (uCTX) and
131 serum osteocalcin, to levels similar to those in premenopausal women. Changes in
132 markers of bone formation were observed later than changes in resorption markers, as
133 expected, due to the coupled nature of bone resorption and formation. Treatment with
134 2.5 mg daily BONIVA decreased levels of uCTX within 1 month of starting treatment
135 and decreased levels of osteocalcin within 3 months. Bone turnover markers reached a
136 nadir of approximately 64% below baseline values by 6 months of treatment and
137 remained stable with continued treatment for up to 3 years. Following treatment
138 discontinuation, there is a return to pretreatment baseline rates of elevated bone
139 resorption associated with postmenopausal osteoporosis.

140 In a 1-year, Phase 3 study comparing once-monthly vs. once-daily oral dosing regimens,
141 the median decrease from baseline in serum CTX values was -76% for patients treated
142 with the 150 mg once-monthly regimen and -67% for patients treated with the 2.5 daily
143 regimen.

144 **CLINICAL STUDIES**

145 **Treatment of Postmenopausal Osteoporosis**

146 The effectiveness and safety of BONIVA were demonstrated in a randomized, double-
147 blind, placebo-controlled, multinational study (Treatment Study) of 2946 women aged 55
148 to 80 years, who were on average 21 years post-menopause, who had lumbar spine BMD
149 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and
150 who had 1 to 4 prevalent vertebral fractures. BONIVA was evaluated at oral doses of 2.5
151 mg daily and 20 mg intermittently. The main outcome measure was the occurrence of
152 new radiographically diagnosed vertebral fractures after 3 years of treatment. The
153 diagnosis of an incident vertebral fracture was based on both qualitative diagnosis by the
154 radiologist and quantitative morphometric criterion. The morphometric criterion required
155 the dual occurrence of 2 events: a relative height ratio or relative height reduction in a
156 vertebral body of at least 20%, together with at least a 4 mm absolute decrease in height.
157 All women received 400 IU vitamin D and 500 mg calcium supplementation per day.

158 The effectiveness and safety of BONIVA once monthly were demonstrated in a
159 randomized, double-blind, multinational, noninferiority trial in 1602 women aged 54 to
160 81 years, who were on average 18 years postmenopause, and had L2-L4 lumbar spine
161 BMD T-score below -2.5 SD at baseline. The main outcome measure was the comparison
162 of the percentage change from baseline in lumbar spine BMD after 1 year of treatment
163 with once-monthly ibandronate (100 mg, 150 mg) to daily ibandronate (2.5 mg). All
164 patients received 400 IU vitamin D and 500 mg calcium supplementation per day.

165 **Effect on Vertebral Fracture**

166 BONIVA 2.5 mg daily significantly reduced the incidence of new vertebral and of new
167 and worsening vertebral fractures. Over the course of the 3-year study, the risk for
168 vertebral fracture was 9.6% in the placebo-treated women and 4.7% in the women treated
169 with BONIVA 2.5 mg ($p < 0.001$) (see Table 1).

170 **Table 1** **Effect of BONIVA on the Incidence of Vertebral Fracture in**
 171 **the 3-Year Osteoporosis Treatment Study***

Proportion of Patients with Fracture (%)				
	Placebo n=975	BONIVA 2.5 mg Daily n=977	Absolute Risk Reduction (%) 95% CI	Relative Risk Reduction (%) 95% CI
New Vertebral Fracture	9.6	4.7	4.9	52**
0-3 Year			(2.3, 7.4)	(29, 68)
New and Worsening Vertebral Fracture	10.4	5.1	5.3	52
0-3 Year			(2.6, 7.9)	(30, 67)
Clinical (Symptomatic) Vertebral Fracture	5.3	2.8	2.5	49
0-3 Year			(0.6, 4.5)	(14, 69)

172 *The endpoint value is the value at the study's last time point, 3 years, for all patients who had a fracture
 173 identified at that time; otherwise, the last post-baseline value prior to the study's last time point is used.

174 **p=0.0003 vs. placebo

175

176 Effect on Nonvertebral Fractures

177 There was a similar number of nonvertebral osteoporotic fractures at 3 years reported in
 178 women treated with BONIVA 2.5 mg daily [9.1%, (95% CI: 7.1%, 11.1%)] and placebo
 179 [8.2%, (95% CI: 6.3%, 10.2%)]. The two treatment groups were also similar with regard
 180 to the number of fractures reported at the individual non-vertebral sites: pelvis, femur,
 181 wrist, forearm, rib, and hip.

182 Effect on Bone Mineral Density (BMD)

183 BONIVA significantly increased BMD at the lumbar spine and hip relative to treatment
 184 with placebo. In the 3-year osteoporosis treatment study, BONIVA 2.5 mg daily
 185 produced increases in lumbar spine BMD that were progressive over 3 years of treatment
 186 and were statistically significant relative to placebo at 6 months and at all later time
 187 points. Lumbar spine BMD increased by 6.4% after 3 years of treatment with 2.5 mg
 188 daily BONIVA compared with 1.4% in the placebo group. Table 2 displays the
 189 significant increases in BMD seen at the lumbar spine, total hip, femoral neck, and
 190 trochanter compared to placebo. Thus, overall BONIVA reverses the loss of BMD, a
 191 central factor in the progression of osteoporosis.

192 **Table 2** **Mean Percent Change in BMD from Baseline to Endpoint in**
 193 **Patients Treated Daily with BONIVA 2.5 mg or Placebo in the**
 194 **3-Year Osteoporosis Treatment Study***

	Placebo	BONIVA 2.5 mg Daily
Lumbar Spine	1.4 (n=693)	6.4 (n=712)
Total Hip	-0.7 (n=638)	3.1 (n=654)
Femoral Neck	-0.7 (n=683)	2.6 (n=699)
Trochanter	0.2 (n=683)	5.3 (n=699)

195 *The endpoint value is the value at the study's last time point, 3 years, for all patients who had BMD
 196 measured at that time; otherwise the last post-baseline value prior to the study's last time point is used.

197
 198 BONIVA 150 mg once-monthly (n=327) was shown to be noninferior to BONIVA
 199 2.5 mg daily (n=318) in lumbar spine BMD in a 1-year, double-blind, multicenter study
 200 of women with postmenopausal osteoporosis. In the primary efficacy analysis (per-
 201 protocol population), the mean increases from baseline in lumbar spine BMD at 1 year
 202 were 3.86% (95% CI: 3.40%, 4.32%) in the 2.5-mg daily group and 4.85% (95% CI:
 203 4.41%, 5.29%) in the 150-mg once-monthly group; the mean difference between 2.5 mg
 204 daily and 150 mg once monthly was 0.99% (95% CI: 0.38%, 1.60%), which was
 205 statistically significant (p=0.002). The results of the intent-to-treat analysis were
 206 consistent with the primary efficacy analysis. The 150 mg once-monthly group also had
 207 consistently higher BMD increases at the other skeletal sites compared to the 2.5 mg
 208 daily group.

209 Bone Histology

210 The effects of BONIVA 2.5 mg daily on bone histology were evaluated in iliac crest
 211 biopsies from 16 women after 22 months of treatment and 20 women after 34 months of
 212 treatment.

213 The histological analysis of bone biopsies showed bone of normal quality and no
 214 indication of osteomalacia or a mineralization defect.

215 Prevention of Postmenopausal Osteoporosis

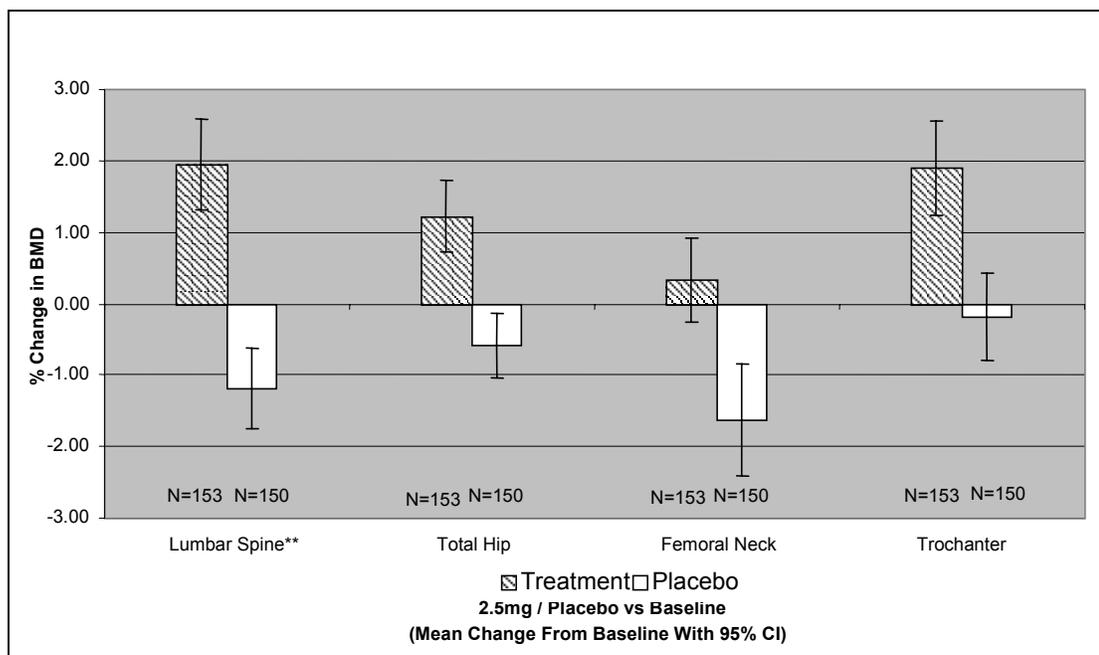
216 BONIVA 2.5 mg daily prevented bone loss in a majority of women in a randomized,
 217 double-blind, placebo-controlled 2-year study (Prevention Study) of 653 postmenopausal
 218 women without osteoporosis at baseline. Women were aged 41 to 82 years, were on

219 average 8.5 years post-menopause, and had lumbar spine BMD T-scores >-2.5 . Women
 220 were stratified according to time since menopause (1 to 3 years, >3 years) and baseline
 221 lumbar spine BMD (T-score: >-1 , -1 to -2.5). The study compared daily BONIVA at
 222 three dose levels (0.5 mg, 1.0 mg, 2.5 mg) with placebo. All women received 500 mg of
 223 supplemental calcium per day.

224 The primary efficacy measure was the change in BMD of lumbar spine after 2 years of
 225 treatment. BONIVA 2.5 mg daily resulted in a mean increase in lumbar spine BMD of
 226 3.1% compared with placebo following 2 years of treatment (see Figure 1). Increases in
 227 BMD were seen at 6 months and at all later time points. Irrespective of the time since
 228 menopause or the degree of pre-existing bone loss, treatment with BONIVA resulted in a
 229 higher BMD response at the lumbar spine compared with placebo across all four baseline
 230 strata [time since menopause (1 to 3 years, >3 years) and baseline lumbar spine BMD
 231 (T-score: >-1 , -1 to -2.5)].

232 Compared with placebo, treatment with BONIVA 2.5 mg daily increased BMD of the
 233 total hip by 1.8%, the femoral neck by 2.0%, and the trochanter by 2.1% (see Figure 1).

234 **Figure 1 Mean Percentage Change in BMD from Baseline to Endpoint**
 235 **in Patients Treated with BONIVA 2.5 mg or Placebo in the**
 236 **2-Year Osteoporosis Prevention Study***



237 *The endpoint value is the value at the study's last time point, 2 years, for all patients who had BMD
 238 measured at that time; otherwise the last postbaseline value prior to the study's last time point is used
 239 **lumbar spine BMD $p<0.001$ vs. placebo

240
 241
 242 The safety and efficacy of once monthly BONIVA 150 mg in postmenopausal women
 243 without osteoporosis are currently being studied, but data are not yet available.

244 **Animal Pharmacology**

245 Animal studies have shown that ibandronate is an inhibitor of osteoclast-mediated bone
246 resorption. In the Schenk assay in growing rats, ibandronate inhibited bone resorption
247 and increased bone volume, based on histologic examination of the tibial metaphyses.
248 There was no evidence of impaired mineralization at the highest dose of 5 mg/kg/day
249 (subcutaneously), which is 1000 times the lowest antiresorptive dose of 0.005 mg/kg/day
250 in this model, and 5000 times the optimal antiresorptive dose of 0.001 mg/kg/day in the
251 aged ovariectomized rat. This indicates that BONIVA administered at therapeutic doses
252 is unlikely to induce osteomalacia.

253 Long-term daily or once-monthly intermittent administration of ibandronate to
254 ovariectomized rats or monkeys was associated with suppression of bone turnover and
255 increases in bone mass. In both rats and monkeys, vertebral BMD, trabecular density, and
256 biomechanical strength were increased dose-dependently at doses up to 15 times the
257 recommended human daily oral dose of 2.5 mg, or cumulative monthly doses up to 8
258 times (rat) or 6 times (monkey) the recommended human once-monthly oral dose of
259 150 mg, based on body surface area (mg/m²) or AUC comparison. In monkeys,
260 ibandronate maintained the positive correlation between bone mass and strength at the
261 ulna and femoral neck. New bone formed in the presence of ibandronate had normal
262 histologic structure and did not show mineralization defects.

263 **INDICATIONS AND USAGE**

264 BONIVA is indicated for the treatment and prevention of osteoporosis in postmenopausal
265 women.

266 **Treatment of Postmenopausal Osteoporosis**

267 In postmenopausal women with osteoporosis, BONIVA increases BMD and reduces the
268 incidence of vertebral fractures (see **CLINICAL STUDIES**). Osteoporosis may be
269 confirmed by the presence or history of osteoporotic fracture or by a finding of low bone
270 mass (BMD more than 2 standard deviations below the premenopausal mean [ie,
271 T-score]).

272 **Prevention of Postmenopausal Osteoporosis**

273 BONIVA may be considered in postmenopausal women who are at risk of developing
274 osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to
275 reduce the risk of fracture.

276 Factors such as family history of osteoporosis, early menopause, previous fracture, high
277 bone turnover, reduced BMD (at least 1.0 SD below the premenopausal mean), thin body
278 frame, Caucasian or Asian race, and smoking, are associated with an increased risk of
279 developing osteoporosis and fractures. The presence of these risk factors may be
280 important when considering the use of BONIVA for preventing osteoporosis.

281 **CONTRAINDICATIONS**

- 282 • Known hypersensitivity to BONIVA or to any of its excipients
- 283 • Uncorrected hypocalcemia (see **PRECAUTIONS: General**)

- 284 • Inability to stand or sit upright for at least 60 minutes (see **DOSAGE AND**
285 **ADMINISTRATION**)
286

287 **WARNINGS**

288 BONIVA, like other bisphosphonates administered orally may cause upper
289 gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer
290 (see **PRECAUTIONS**).

291 **PRECAUTIONS**

292 **General**

293 Mineral Metabolism

294 Hypocalcemia and other disturbances of bone and mineral metabolism should be
295 effectively treated before starting BONIVA therapy. Adequate intake of calcium and
296 vitamin D is important in all patients.

297 Upper Gastrointestinal Effects

298 Bisphosphonates administered orally have been associated with dysphagia, esophagitis,
299 and esophageal or gastric ulcers. This association has been reported for bisphosphonates
300 in postmarketing experience but has not been found in most preapproval clinical trials,
301 including those conducted with BONIVA. Therefore, patients should be advised to pay
302 particular attention to and be able to comply with the dosing instructions to minimize the
303 risk of these effects (see **DOSAGE AND ADMINISTRATION**).

304 Severe Renal Impairment

305 BONIVA is not recommended for use in patients with severe renal impairment
306 (creatinine clearance <30 mL/min).

307 Jaw Osteonecrosis

308 Osteonecrosis, primarily in the jaw, has been reported in patients treated with
309 bisphosphonates. Most cases have been in cancer patients undergoing dental procedures,
310 but some have occurred in patients with postmenopausal osteoporosis or other diagnoses.
311 Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies
312 (e.g., chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (e.g.,
313 anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have
314 been in patients treated with bisphosphonates intravenously but some have been in
315 patients treated orally.

316 For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate
317 therapy, dental surgery may exacerbate the condition. For patients requiring dental
318 procedures, there are no data available to suggest whether discontinuation of
319 bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating
320 physician should guide the management plan of each patient based on individual
321 benefit/risk assessment.

322 Musculoskeletal Pain

323 In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or
324 muscle pain has been reported in patients taking bisphosphonates that are approved for
325 the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS**). However,
326 such reports have been infrequent. This category of drugs include BONIVA (ibandronate
327 sodium) Tablets. Most of the patients were postmenopausal women. The time to onset of
328 symptoms varied from one day to several months after starting the drug. Most patients
329 had relief of symptoms after stopping. A subset had recurrence of symptoms when
330 rechallenged with the same drug or another bisphosphonate.

331 In placebo-controlled studies with BONIVA, the percentages of patients with these
332 symptoms were similar in the BONIVA and placebo groups.

333 Information for Patients

334 Patients should be instructed to read the Patient Information Leaflet carefully before
335 taking BONIVA, to re-read it each time the prescription is renewed and to pay particular
336 attention to the dosing instructions in order to maximize absorption and clinical benefit.

337 - BONIVA should be taken at least 60 minutes before the first food or drink (other than
338 water) of the day and before taking any oral medications containing multivalent
339 cations (including antacids, supplements or vitamins).

340 - To facilitate delivery to the stomach, and thus reduce the potential for esophageal
341 irritation, BONIVA tablets should be swallowed whole with a full glass of plain water
342 (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients
343 should not lie down for 60 minutes after taking BONIVA.

344 - Plain water is the only drink that should be taken with BONIVA. Please note that
345 some mineral waters may have a higher concentration of calcium and therefore
346 should not be used.

347 - Patients should not chew or suck the tablet because of a potential for oropharyngeal
348 ulceration.

349 - The BONIVA 150-mg tablet should be taken on the same date each month (ie, the
350 patient's BONIVA day).

351 - If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is
352 more than 7 days away, the patient should be instructed to take one BONIVA 150-mg
353 tablet in the morning following the date that it is remembered (see **DOSAGE AND**
354 **ADMINISTRATION**). The patient should then return to taking one BONIVA
355 150-mg tablet every month in the morning of their chosen day, according to their
356 original schedule.

357 - The patient must not take two 150-mg tablets within the same week. If the patient's
358 next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until
359 their next scheduled BONIVA day to take their tablet. The patient should then return
360 to taking one BONIVA 150-mg tablet every month in the morning of their chosen
361 day, according to their original schedule.

362 Patients should receive supplemental calcium and vitamin D if dietary intake is
363 inadequate. Intake of supplemental calcium and vitamin D should be delayed for at least
364 60 minutes following oral administration of BONIVA in order to maximize absorption of
365 BONIVA.

366 Physicians should be alert to signs or symptoms signaling a possible esophageal reaction
367 during therapy, and patients should be instructed to discontinue BONIVA and seek
368 medical attention if they develop symptoms of esophageal irritation such as new or
369 worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

370 **Drug Interactions**

371 See CLINICAL PHARMACOLOGY: Pharmacokinetics: Drug Interactions.

372 **Calcium Supplements/Antacids**

373 Products containing calcium and other multivalent cations (such as aluminum,
374 magnesium, iron) are likely to interfere with absorption of BONIVA. BONIVA should be
375 taken at least 60 minutes before any oral medications containing multivalent cations
376 (including antacids, supplements or vitamins) (see **PRECAUTIONS: Information for**
377 **Patients**).

378 **H2 Blockers and Proton Pump Inhibitors (PPIs)**

379 Of over 3500 patients enrolled in the BONIVA osteoporosis Treatment and Prevention
380 Studies, 15% used anti-peptic agents (primarily H2 blockers and PPIs). Among these
381 patients, the incidence of upper gastrointestinal adverse experiences in the patients treated
382 with BONIVA was similar to that in placebo-treated patients. Similarly, of over 1600
383 patients enrolled in a study comparing once-monthly with daily dosing regimens of
384 ibandronate, 14% of patients used anti-peptic agents. Among these patients, the incidence
385 of upper gastrointestinal adverse experiences in the patients treated with BONIVA
386 150 mg once monthly was similar to that in patients treated with BONIVA 2.5 mg once
387 daily.

388 **Aspirin/Nonsteroidal Antiinflammatory Drugs (NSAIDs)**

389 In the large, placebo-controlled osteoporosis Treatment Study, aspirin and nonsteroidal
390 antiinflammatory drugs were taken by 62% of the 2946 patients. Among aspirin or
391 NSAID users, the incidence of upper gastrointestinal adverse events in patients treated
392 with ibandronate 2.5 mg daily (28.9%) was similar to that in placebo-treated patients
393 (30.7%). Similarly, in the 1-year monthly comparison study, aspirin and nonsteroidal
394 antiinflammatory drugs were taken by 39% of the 1602 patients. The incidence of upper
395 gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in
396 patients taking ibandronate 2.5 mg daily (21.7%) and 150 mg once monthly (22.0%).
397 However, since aspirin, NSAIDs, and bisphosphonates are all associated with
398 gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or
399 NSAIDs with BONIVA.

400 **Drug/Laboratory Test Interactions**

401 Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific
402 studies with ibandronate have not been performed.

403 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

404 **Carcinogenesis**

405 In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered
406 by oral gavage to male and female Wistar rats (systemic exposures up to 12 and 7 times,
407 respectively, human exposure at the recommended daily oral dose of 2.5 mg, and
408 cumulative exposures up to 3.5 and 2 times, respectively, human exposure at the
409 recommended once-monthly oral dose of 150 mg, based on AUC comparison). There
410 were no significant drug-related tumor findings in male or female rats. In a 78-week
411 carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage
412 to male and female NMRI mice (exposures up to 475 and 70 times, respectively, human
413 exposure at the recommended daily oral dose of 2.5 mg and cumulative exposures up to
414 135 and 20 times, respectively, human exposure at the recommended once-monthly oral
415 dose of 150 mg, based on AUC comparison). There were no significant drug-related
416 tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5,
417 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice (cumulative
418 monthly exposures in males and females up to 70 and 115 times, respectively, human
419 exposure at the recommended dose of 150 mg, based on AUC comparison). A dose-
420 related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in
421 female mice, which was statistically significant at 80 mg/kg/day (220 to 400 times human
422 exposure at the recommended daily oral dose of 2.5 mg and 115 times human exposure at
423 the recommended once-monthly oral dose of 150 mg, based on AUC comparison). The
424 relevance of these findings to humans is unknown.

425 **Mutagenesis**

426 There was no evidence for a mutagenic or clastogenic potential of ibandronate in the
427 following assays: in vitro bacterial mutagenesis assay in *Salmonella typhimurium* and
428 *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79
429 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and
430 without metabolic activation. Ibandronate was not genotoxic in the in vivo mouse
431 micronucleus tests for chromosomal damage.

432 **Impairment of Fertility**

433 In female rats treated from 14 days prior to mating through gestation, decreases in
434 fertility, corpora lutea, and implantation sites were observed at an oral dose of 16
435 mg/kg/day (45 times human exposure at the recommended daily oral dose of 2.5 mg and
436 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based
437 on AUC comparison).

438 **Pregnancy**

439 **Pregnancy Category C**

440 In female rats given oral doses of 1, 4, or 16 mg/kg/day beginning 14 days before mating
441 and continuing through lactation, maternal deaths were observed at the time of delivery in
442 all dose groups (≥ 3 times human exposure at the recommended daily oral dose of 2.5 mg
443 or ≥ 1 times human exposure at the recommended once-monthly oral dose of 150 mg,
444 based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times
445 human exposure at the recommended daily oral dose of 2.5 mg and 13 times human
446 exposure at the recommended once-monthly oral dose of 150 mg, based on AUC
447 comparison) was likely related to maternal dystocia. In pregnant rats given oral doses of
448 6, 20, or 60 mg/kg/day during gestation, calcium supplementation (32 mg/kg/day by
449 subcutaneous injection from gestation day 18 to parturition) did not completely prevent
450 dystocia and periparturient mortality in any of the treated groups (≥ 16 times human
451 exposure at the recommended daily oral dose of 2.5 mg and ≥ 4.6 times human exposure
452 at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). A
453 low incidence of postimplantation loss was observed in rats treated from 14 days before
454 mating throughout lactation or during gestation, only at doses causing maternal dystocia
455 and periparturient mortality. In pregnant rats dosed orally with 1, 5, or 20 mg/kg/day
456 from gestation day 17 through lactation day 21 (following closure of the hard palate
457 through weaning), maternal toxicity, including dystocia and mortality, fetal perinatal and
458 postnatal mortality, were observed at doses ≥ 5 mg/kg/day (equivalent to human exposure
459 at the recommended daily oral dose of 2.5 mg and ≥ 4 times human exposure at the
460 recommended once-monthly oral dose of 150 mg, based on AUC comparison).
461 Periparturient mortality has also been observed with other bisphosphonates and appears
462 to be a class effect related to inhibition of skeletal calcium mobilization resulting in
463 hypocalcemia and dystocia.

464 Exposure of pregnant rats during the period of organogenesis resulted in an increased
465 fetal incidence of RPU (renal pelvis ureter) syndrome at oral doses ≥ 10 mg/kg/day (≥ 30
466 times human exposure at the recommended daily oral dose of 2.5 mg and ≥ 9 times human
467 exposure at the recommended once-monthly oral dose of 150 mg, based on AUC
468 comparison). Impaired pup neuromuscular development (cliff avoidance test) was
469 observed at 16 mg/kg/day when dams were dosed from 14 days before mating through
470 lactation (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13
471 times human exposure at the recommended once-monthly oral dose of 150 mg, based on
472 AUC comparison).

473 In pregnant rabbits given oral doses of 1, 4, or 20 mg/kg/day during gestation, dose-
474 related maternal mortality was observed in all treatment groups (≥ 8 times the
475 recommended human daily oral dose of 2.5 mg and ≥ 4 times the recommended human
476 once-monthly oral dose of 150 mg, based on body surface area comparison, mg/m^2). The
477 deaths occurred prior to parturition and were associated with lung edema and
478 hemorrhage. No significant fetal anomalies were observed.

479 Bisphosphonates are incorporated into the bone matrix, from where they are gradually
480 released over periods of weeks to years. The extent of bisphosphonate incorporation into

481 adult bone, and hence, the amount available for release back into the systemic circulation,
482 is directly related to the total dose and duration of bisphosphonate use. Although there are
483 no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and
484 animal data suggest that uptake of bisphosphonates into fetal bone is greater than into
485 maternal bone. Therefore, there is a theoretical risk of fetal harm (eg, skeletal and other
486 abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate
487 therapy. The impact of variables such as time between cessation of bisphosphonate
488 therapy to conception, the particular bisphosphonate used, and the route of administration
489 (intravenous versus oral) on this risk has not been established.

490 There are no adequate and well-controlled studies in pregnant women. BONIVA should
491 be used during pregnancy only if the potential benefit justifies the potential risk to the
492 mother and fetus.

493 **Nursing Mothers**

494 In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in
495 breast milk at concentrations of 8.1 to 0.4 ng/mL from 2 to 24 hours after dose
496 administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is
497 not known whether BONIVA is excreted in human milk. Because many drugs are
498 excreted in human milk, caution should be exercised when BONIVA is administered to a
499 nursing woman.

500 **Pediatric Use**

501 Safety and effectiveness in pediatric patients have not been established.

502 **Geriatric Use**

503 Of the patients receiving BONIVA 2.5 mg daily in postmenopausal osteoporosis studies,
504 52% were over 65 years of age, and 10% were over 75 years of age. Of the patients
505 receiving BONIVA 150 mg once monthly in the postmenopausal osteoporosis 1-year
506 study, 52% were over 65 years of age, and 9% were over 75 years of age. No overall
507 differences in effectiveness or safety were observed between these patients and younger
508 patients but greater sensitivity in some older individuals cannot be ruled out.

509 **ADVERSE REACTIONS**

510 **Daily Dosing**

511 Daily treatment with oral BONIVA was studied in over 3900 patients in postmenopausal
512 osteoporosis trials of up to 3 years duration. The overall adverse event profile of
513 BONIVA 2.5 mg once daily in these studies was similar to that of placebo.

514 **Treatment and Prevention of Postmenopausal Osteoporosis**

515 Most adverse events were mild or moderate and did not lead to discontinuation. The
516 incidence of serious adverse events was 20% in the placebo group and 23% in the
517 BONIVA 2.5 mg daily group. The percentage of patients who withdrew from treatment
518 due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily group
519 and the placebo group. Overall, and according to body system, there was no difference

520 between BONIVA and placebo, with adverse events of the digestive system being the
521 most common reason for withdrawal.

522 Table 3 lists adverse events from the Treatment and Prevention Studies reported in $\geq 2\%$
523 of patients and in more patients treated daily with BONIVA than patients treated with
524 placebo. Adverse events are shown without attribution of causality.

525 **Table 3** **Adverse Events Occurring at a Frequency $\geq 2\%$ and in More**
526 **Patients Treated with BONIVA than in Patients Treated with**
527 **Placebo Daily in the Osteoporosis Treatment and Prevention**
528 **Studies**

Body System	Placebo % (n=1134)	BONIVA 2.5 mg % (n=1140)
Body as a Whole		
Back Pain	12.2	13.5
Pain in Extremity	6.4	7.8
Infection	3.4	4.3
Asthenia	2.3	3.5
Allergic Reaction	1.9	2.5
Digestive System		
Dyspepsia	9.8	11.9
Diarrhea	5.0	6.8
Tooth Disorder	2.3	3.5
Vomiting	2.1	2.7
Gastritis	1.9	2.2
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.2	4.8
Musculoskeletal System		
Myalgia	5.1	5.7
Joint Disorder	3.3	3.6
Arthritis	2.7	3.2
Nervous System		
Headache	5.8	6.5
Dizziness	2.6	3.7
Vertigo	2.5	3.0
Nerve Root Lesion	1.9	2.2
Respiratory System		
Upper Respiratory Infection	33.2	33.7
Bronchitis	6.8	10.0
Pneumonia	4.3	5.9
Pharyngitis	1.5	2.5
Urogenital System		
Urinary Tract Infection	4.2	5.5

529

530 **Once Monthly Dosing**

531 In a 1-year, double-blind, multicenter study comparing BONIVA 2.5 mg once daily and
 532 BONIVA 150 mg once monthly in women with postmenopausal osteoporosis, the overall
 533 safety and tolerability profiles of the two oral dosing regimens were similar. The
 534 incidence of serious adverse events was 4.8% in the BONIVA 2.5 mg daily group and
 535 7.1% in the BONIVA 150 mg once monthly group. The percentage of patients who
 536 withdrew from treatment due to adverse events was approximately 8.9% in the BONIVA
 537 2.5 mg daily group and 7.8% in the BONIVA 150 mg once monthly group. Table 4 lists
 538 the adverse events reported in $\geq 2\%$ of patients without attribution of causality.

539 **Table 4 Adverse Events With an Incidence of at Least 2% in Patients**
 540 **Treated with BONIVA 150 mg Once Monthly or 2.5 mg Daily**

Body System/Adverse Event	BONIVA 2.5 mg daily % (n=395)	BONIVA 150 mg monthly % (n=396)
Vascular Disorders		
Hypertension	7.3	6.3
Gastrointestinal Disorders		
Dyspepsia	7.1	5.6
Nausea	4.8	5.1
Diarrhea	4.1	5.1
Constipation	2.5	4.0
Abdominal pain ^a	5.3	7.8
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3.5	5.6
Back Pain	4.3	4.5
Pain in extremity	1.3	4.0
Localized osteoarthritis	1.3	3.0
Myalgia	0.8	2.0
Muscle cramp	2.0	1.8
Infections and Infestations		
Influenza	3.8	4.0
Nasopharyngitis	4.3	3.5
Bronchitis	3.5	2.5
Urinary tract infection	1.8	2.3
Upper respiratory tract infection	2.0	2.0
Nervous System Disorders		
Headache	4.1	3.3
Dizziness	1.0	2.3
General Disorders and Administration Site Conditions		
Influenza-like illness ^b	0.8	3.3
Skin and Subcutaneous Tissue		

Disorders		
Rash ^c	1.3	2.3
Psychiatric Disorders		
Insomnia	0.8	2.0
^a Combination of abdominal pain and abdominal pain upper ^b Combination of influenza-like illness and acute phase reaction ^c Combination of rash pruritic, rash macular, rash papular, rash generalized, rash erythematous, dermatitis, dermatitis allergic, dermatitis medicamentosa, erythema and exanthem		

541

542 Patients with a previous history of gastrointestinal disease, including patients with peptic
543 ulcer without recent bleeding or hospitalization and patients with dyspepsia or reflux
544 controlled by medication, were included in the once monthly treatment study. For these
545 patients, there was no difference in upper gastrointestinal adverse events with the 150 mg
546 once monthly regimen compared to the 2.5 mg once daily regimen.

547 **Ocular Adverse Events**

548 Reports in the medical literature indicate that bisphosphonates may be associated with
549 ocular inflammation such as uveitis and scleritis. In some cases, these events did not
550 resolve until the bisphosphonate was discontinued. There were no reports of ocular
551 inflammation in studies with BONIVA 2.5 mg daily. Two patients who received
552 BONIVA monthly experienced ocular inflammation, one was a case of uveitis and the
553 other scleritis.

554 **Laboratory Test Findings**

555 In the 3-year treatment study with BONIVA 2.5 mg daily, there were no clinically
556 significant changes from baseline values or shifts in any laboratory variable for each of
557 the treatment groups. As expected with bisphosphonate treatment, a decrease in total
558 alkaline phosphatase levels was seen in the active treatment groups compared to placebo.
559 There was no difference compared with placebo for laboratory abnormalities indicative
560 of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia. Similarly, no
561 changes were noted for the 150 mg once monthly administration in the 1-year study.

562 **OVERDOSAGE**

563 No specific information is available on the treatment of overdosage with BONIVA.
564 However, based on knowledge of this class of compounds, oral overdosage may result in
565 hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as
566 upset stomach, dyspepsia, esophagitis, gastritis, or ulcer. Milk or antacids should be
567 given to bind BONIVA. Due to the risk of esophageal irritation, vomiting should not be
568 induced, and the patient should remain fully upright. Dialysis would not be beneficial.

569 **DOSAGE AND ADMINISTRATION**

570 The recommended dose of BONIVA for treatment of postmenopausal osteoporosis is one
571 2.5-mg tablet taken once daily or one 150 mg tablet taken once monthly on the same date
572 each month (see **INDICATIONS AND USAGE**).

573 The recommended dose of BONIVA for the prevention of postmenopausal osteoporosis
574 is one 2.5-mg tablet taken once-daily. Alternatively, one 150-mg tablet taken once
575 monthly on the same date each month may be considered (see **INDICATIONS AND**
576 **USAGE**).

577 - To maximize absorption and clinical benefit, BONIVA should be taken at least 60
578 minutes before the first food or drink (other than water) of the day or before taking
579 any oral medication or supplementation, including calcium, antacids, or vitamins (see
580 **PRECAUTIONS: Information for Patients and Drug Interactions**).

581 - To facilitate delivery to the stomach and thus reduce the potential for esophageal
582 irritation, BONIVA tablets should be swallowed whole with a full glass of plain water
583 (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients
584 should not lie down for 60 minutes after taking BONIVA (see **PRECAUTIONS:**
585 **General and Information for Patients**).

586 - Plain water is the only drink that should be taken with BONIVA. Please note that
587 some mineral waters may have a higher concentration of calcium and therefore
588 should not be used.

589 - Patients should not chew or suck the tablet because of a potential for oropharyngeal
590 ulceration.

591 - The BONIVA 150-mg tablet should be taken on the same date each month (ie, the
592 patient's BONIVA day).

593 - If the once monthly dose is missed, and the patient's next scheduled BONIVA day is
594 more than 7 days away, the patient should be instructed to take one BONIVA 150-mg
595 tablet in the morning following the date that it is remembered. The patient should
596 then return to taking one BONIVA 150-mg tablet every month in the morning of their
597 chosen day, according to their original schedule.

598 - The patient must not take two 150-mg tablets within the same week. If the patient's
599 next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until
600 their next scheduled BONIVA day to take their tablet. The patient should then return
601 to taking one BONIVA 150-mg tablet every month in the morning of their chosen
602 day, according to their original schedule.

603 Patients should receive supplemental calcium or vitamin D if dietary intake is inadequate
604 (see **PRECAUTIONS: Information for Patients**).

605 **Patients with Hepatic Impairment**

606 No dose adjustment is necessary (see **CLINICAL PHARMACOLOGY: Special**
607 **Populations**).

608 **Patients with Renal Impairment**

609 No dose adjustment is necessary for patients with mild or moderate renal impairment
610 where creatinine clearance is equal to or greater than 30 mL/min.

611 BONIVA is not recommended for use in patients with severe renal impairment
 612 (creatinine clearance of <30 mL/min) (see **CLINICAL PHARMACOLOGY: Special**
 613 **Populations**).

614 **Geriatric Patients**

615 No dosage adjustment is necessary in the elderly (see **PRECAUTIONS: Geriatric Use**).

616 **HOW SUPPLIED**

617 BONIVA 2.5 mg tablets: supplied as white, oblong, film-coated tablets, engraved with
 618 "IT" on one side and "L3" on the other side and packaged in bottles of 30 tablets (NDC
 619 0004-0185-23).

620 BONIVA 150 mg tablets: supplied as white, oblong, film-coated tablets, engraved with
 621 "BNVA" on one side and "150" on the other side. Packaged in boxes of 3 blister packs
 622 containing 1 tablet each (NDC 0004-0186-82).

623 **Storage**

624 Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see
 625 USP Controlled Room Temperature].

626

627 BONIVA is a registered trademark of Roche Therapeutics Inc.

628

629 Distributed by:

630



Pharmaceuticals

Roche Laboratories Inc.
 340 Kingsland Street
 Nutley, New Jersey 07110-1199

631

632 Co-promoted by Roche Laboratories Inc. and

633



GlaxoSmithKline

GlaxoSmithKline
 Research Triangle Park, NC 27709

634

635

636

637

638 27898798

639 27898925

640 Issued: March 2005

641 Copyright © 2005 by Roche Laboratories Inc. All rights reserved.



1

2

3

Patient Information

4

5

BONIVA[®] [bon-EE-va] (ibandronate sodium) TABLETS

6

7

8

9

R_x only

10 Read this patient information carefully before you start taking BONIVA. Read this
11 patient information each time you get a refill for BONIVA. There may be new
12 information. This information is not everything you need to know about BONIVA. It
13 does not take the place of talking with your health care provider about your condition or
14 your treatment. Talk about BONIVA with your health care provider before you start
15 taking it, and at your regular check-ups.

16 What is the most important information I should know about BONIVA?

17 BONIVA may cause serious problems in the stomach and the esophagus (the tube that
18 connects your mouth and stomach) such as trouble swallowing, heartburn, and ulcers (see
19 “**What are the possible side effects of BONIVA?**”).

20 **You must take BONIVA exactly as prescribed for BONIVA to work for you and to**
21 **lower the chance of serious side effects (see “How should I take BONIVA?”).**

22 What is BONIVA?

23 BONIVA is a prescription medicine used to treat or prevent osteoporosis in women after
24 menopause (see the end of this leaflet for “**What is osteoporosis?**”).

25 BONIVA may reverse bone loss by stopping more loss of bone and increasing bone mass
26 in most women who take it, even though they won’t be able to see or feel a difference.
27 BONIVA may help lower the chances of breaking bones (fractures).

28 For BONIVA to treat or prevent osteoporosis, you have to take it as prescribed.
29 BONIVA will not work if you stop taking it.

30 Who should not take BONIVA?

31 Do not take BONIVA if you:

- 32 • have low blood calcium (hypocalcemia)
- 33 • cannot sit or stand up for at least 1 hour (60 minutes)
- 34 • have kidneys that work very poorly

- 35 • are allergic to ibandronate sodium or any of the other ingredients of BONIVA (see
 36 the end of this leaflet for a list of all the ingredients in BONIVA)
 37

38 **Tell your health care provider before using BONIVA:**

- 39 • if you are pregnant or planning to become pregnant. It is not known if BONIVA can
 40 harm your unborn baby.
 41 • if you are breast-feeding. It is not known if BONIVA passes into your milk and if it
 42 can harm your baby.
 43 • have swallowing problems or other problems with your esophagus (the tube that
 44 connects your mouth and stomach)
 45 • if you have kidney problems
 46 • **about all the medicines you take** including prescription and non-prescription
 47 medicines, vitamins and supplements. Some medicines, especially certain vitamins,
 48 supplements, and antacids can stop BONIVA from getting to your bones. This can
 49 happen if you take other medicines too close to the time that you take BONIVA (see
 50 **“How should I take BONIVA?”**).
 51

52 **How should I take BONIVA?**

- 53 • Take BONIVA exactly as instructed by your health care provider.
 54 • Take BONIVA first thing in the morning at least 1 hour (60 minutes) before you eat,
 55 drink anything other than plain water, or take any other oral medicine.
 56 • Take BONIVA with 6 to 8 ounces (about 1 full cup) of plain water. Do not take it
 57 with any other drink besides plain water. Do not take it with other drinks, such as
 58 mineral water, sparkling water, coffee, tea, dairy drinks (such as milk), or juice.
 59 • Swallow BONIVA whole. Do not chew or suck the tablet or keep it in your mouth to
 60 melt or dissolve.
 61 • After taking BONIVA you must wait at least 1 hour (60 minutes) before:
 62
 63 – Lying down. You may sit, stand, or do normal activities like read the newspaper
 64 or take a walk.
 65 – Eating or drinking anything except for plain water.
 66 – Taking other oral medicines including vitamins, calcium, or antacids. Take your
 67 vitamins, calcium, and antacids at a different time of the day from the time when
 68 you take BONIVA.
 69 • If you take too much BONIVA, drink a full glass of milk and call your local poison
 70 control center or emergency room right away. Do not make yourself vomit. Do not
 71 lie down.
 72 • Keep taking BONIVA for as long as your health care provider tells you. BONIVA
 73 will not work if you stop taking it.
 74 • Your health care provider may tell you to exercise and take calcium and vitamin
 75 supplements to help your osteoporosis.

- 76 • Your health care provider may do a test to measure the thickness (density) of your
77 bones or do other tests to check your progress.

78 **What is my BONIVA schedule?**

79 **Schedule for taking BONIVA 150 mg once monthly:**

- 80 • Take one BONIVA 150-mg tablet once a month.
81 • Choose one date of the month (your BONIVA day) that you will remember and that
82 best fits your schedule to take your BONIVA 150-mg tablet.
83 • Take one BONIVA 150-mg tablet in the morning of your chosen day (see “**How**
84 **should I take BONIVA?**”).
85

86 **What to do if I miss a monthly dose:**

- 87 • If your next scheduled BONIVA day is more than 7 days away, take one BONIVA
88 150-mg tablet in the morning following the day that you remember (see “**How**
89 **should I take BONIVA?**”). Then return to taking one BONIVA 150-mg tablet every
90 month in the morning of your chosen day, according to your original schedule.
91
92 • **Do not** take two 150 mg tablets within the same week. If your next scheduled
93 BONIVA day is only 1 to 7 days away, **wait** until your next scheduled BONIVA day
94 to take your tablet. Then return to taking one BONIVA 150-mg tablet every month in
95 the morning of your chosen day, according to your original schedule.
96
97 • **If you are not sure what to do if you miss a dose, contact your health care**
98 **provider who will be able to advise you.**
99

100 **Schedule for taking BONIVA 2.5 mg once daily:**

- 101 • Take one BONIVA 2.5-mg tablet once a day first thing in the morning at least 1 hour
102 (60 minutes) before you eat, drink anything other than plain water, or take any other
103 oral medicine (see “**How should I take BONIVA?**”).
104

105 **What to do if I miss a daily dose:**

- 106 • If you forget to take your BONIVA 2.5-mg tablet in the morning, **do not** take it later
107 in the day. Just return to your normal schedule and take 1 tablet the next morning. **Do**
108 **not** take two tablets on the same day.
109
110 • **If you are not sure what to do if you miss a dose, contact your health care**
111 **provider who will be able to advise you.**
112

113 **What should I avoid while taking BONIVA?**

- 114 • Do not take other medicines, or eat or drink anything but plain water before you take
115 BONIVA and for at least 1 hour (60 minutes) after you take it.
116 • Do not lie down for at least 1 hour (60 minutes) after you take BONIVA.
117

118 **What are the possible side effects of BONIVA?**

119 **Stop taking BONIVA and call your health care provider right away if you have:**

- 120 • **pain or trouble with swallowing**
121 • **chest pain**
122 • **very bad heartburn or heartburn that does not get better**
123

124 **BONIVA MAY CAUSE:**

- 125 • **pain or trouble swallowing (dysphagia)**
126 • **heartburn (esophagitis)**
127 • **ulcers in your stomach or esophagus (the tube that connects your mouth and stomach)**
128

129 **Common side effects with BONIVA are:**

- 130 • **diarrhea**
131 • **pain in extremities (arms or legs)**
132 • **dyspepsia (upset stomach)**
133

134 **Less common side effects with BONIVA are short-lasting, mild flu-like symptoms**
135 **(usually improve after the first dose). These are not all the possible side effects of**
136 **BONIVA. For more information ask your health care provider or pharmacist.**

137 **Rarely, patients have reported severe bone, joint, and/or muscle pain starting within one**
138 **day to several months after beginning to take, by mouth, bisphosphonate drugs to treat**
139 **osteoporosis (thin bones). This group of drugs includes BONIVA. Most patients**
140 **experienced relief after stopping the drug. Contact your health care provider if you**
141 **develop these symptoms after starting BONIVA.**

142 **What is osteoporosis?**

143 **Osteoporosis is a disease that causes bones to become thinner. Thin bones can break**
144 **easily. Most people think of their bones as being solid like a rock. Actually, bone is**
145 **living tissue, just like other parts of the body, such as your heart, brain, or skin. Bone just**
146 **happens to be a harder type of tissue. Bone is always changing. Your body keeps your**
147 **bones strong and healthy by replacing old bone with new bone.**

148 **Osteoporosis causes the body to remove more bone than it replaces. This means that**
149 **bones get weaker. Weak bones are more likely to break. Osteoporosis is a bone disease**
150 **that is quite common in women after menopause. At first, osteoporosis has no symptoms,**
151 **but people with osteoporosis may develop loss of height and are more likely to break**
152 **(fracture) their bones, especially the back (spine), wrist, and hip bones.**

153 **Osteoporosis can be prevented, and with proper therapy it can be treated.**

154 **Who is at risk for osteoporosis?**

155 **Talk to your health care provider about your chances for getting osteoporosis.**

156 Many things put people at risk for osteoporosis. The following people have a higher
157 chance of getting osteoporosis:

158 Women who:

- 159 • are going through or who are past menopause (“the change”)
- 160 • are white (Caucasian) or Oriental (Asian)

161

162 People who:

- 163 • are thin
- 164 • have a family member with osteoporosis
- 165 • do not get enough calcium or vitamin D
- 166 • do not exercise
- 167 • smoke
- 168 • drink alcohol often
- 169 • take bone thinning medicines (like prednisone) for a long time

170

171 **General information about BONIVA**

172 Medicines are sometimes prescribed for conditions that are not mentioned in patient
173 information. Do not use BONIVA for a condition for which it was not prescribed. Do
174 not give BONIVA to other people, even if they have the same symptoms you have. It
175 may harm them.

176 Store BONIVA at 77°F (25°C) or at room temperature between 59°F and 86°F (15°C and
177 30°C).

178 Keep BONIVA and all medicines out of the reach of children.

179 This summarizes the most important information about BONIVA. If you would like
180 more information, talk with your health care provider. You can ask your health care
181 provider or pharmacist for information about BONIVA that is written for health
182 professionals.

183 For more information about BONIVA, call 1-888-MY-BONIVA or visit
184 www.myboniva.com.

185 **What are the ingredients of BONIVA?**

186 BONIVA (active ingredient): ibandronate sodium

187 BONIVA (inactive ingredients): lactose monohydrate, povidone, microcrystalline
188 cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified
189 water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene
190 glycol 6000 and purified water.

191

192 BONIVA is a registered trademark of Roche Therapeutics Inc.

193

194 Distributed by:

195



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

196

197

198 Co-promoted by Roche Laboratories Inc. and

199



GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709

200

201

202

203

204 27898799

205 27898926

206 Issued: March 2005

207 Copyright © 2005 by Roche Laboratories Inc. All rights reserved.

208

209