



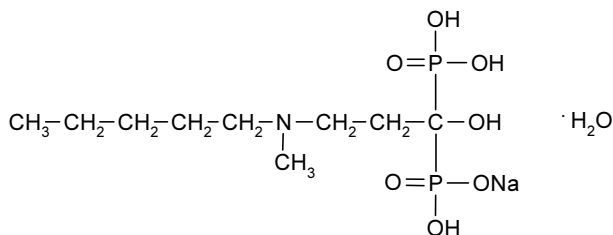
**BONIVA<sup>®</sup>**  
**(ibandronate sodium)**  
**INJECTION**

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6 **R<sub>x</sub> 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 C<sub>9</sub>H<sub>22</sub>NO<sub>7</sub>P<sub>2</sub>Na·H<sub>2</sub>O 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 Injection is intended for intravenous administration only. BONIVA Injection is  
17 available as a sterile, clear, colorless, ready-to-use solution in a prefilled syringe that  
18 delivers 3.375 mg of ibandronate monosodium salt monohydrate in 3 mL of solution,  
19 equivalent to a dose of 3 mg ibandronate free acid. Inactive ingredients include sodium  
20 chloride, glacial acetic acid, sodium acetate and water.

21 **CLINICAL PHARMACOLOGY**

22 **Mechanism of Action**

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

27 **Pharmacokinetics**

28 **Distribution**

29 Area under the serum ibandronate concentrations versus time curve increases in a  
30 dose-proportional manner after administration of 2 mg to 6 mg by intravenous injection.

31 After administration, ibandronate either rapidly binds to bone or is excreted into urine. In  
32 humans, the apparent terminal volume of distribution is at least 90 L, and the amount of  
33 dose removed from the circulation into the bone is estimated to be 40% to 50% of the  
34 circulating dose. In vitro protein binding in human serum was approximately 86% over  
35 an ibandronate concentration range of 20 to 2000 ng/mL (approximate range of  
36 maximum serum ibandronate concentrations upon intravenous bolus administration) in  
37 one study.

### 38 Metabolism

39 There is no evidence that ibandronate is metabolized in humans. Ibandronate does not  
40 inhibit human P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 isozymes in vitro.

### 41 Elimination

42 The portion of ibandronate that is not removed from the circulation via bone absorption is  
43 eliminated unchanged by the kidney (approximately 50% to 60% of the administered  
44 intravenous dose).

45 The plasma elimination of ibandronate is multiphasic. Its renal clearance and distribution  
46 into bone accounts for a rapid and early decline in plasma concentrations, reaching 10%  
47 of  $C_{max}$  within 3 or 8 hours after intravenous or oral administration, respectively. This is  
48 followed by a slower clearance phase as ibandronate redistributes back into the blood  
49 from bone. The observed apparent terminal half-life for ibandronate is generally  
50 dependent on the dose studied and on assay sensitivity. The observed apparent terminal  
51 half-life for intravenous 2 and 4 mg ibandronate after 2 hours of infusion ranges from 4.6  
52 to 15.3 hours and 5 to 25.5 hours, respectively.

53 Following intravenous administration, total clearance of ibandronate is low, with average  
54 values in the range 84 to 160 mL/min. Renal clearance (about 60 mL/min in healthy  
55 postmenopausal women) accounts for 50% to 60% of total clearance and is related to  
56 creatinine clearance. The difference between the apparent total and renal clearances likely  
57 reflects bone uptake of the drug.

### 58 Special Populations

#### 59 Pediatrics

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

#### 61 Gender

62 The pharmacokinetics of ibandronate is similar in both men and women.

#### 63 Geriatric

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

68 **Race**

69 Pharmacokinetic differences due to race have not been studied.

70 **Renal Impairment**

71 Renal clearance of ibandronate in patients with various degrees of renal impairment is  
72 linearly related to creatinine clearance (CL<sub>cr</sub>).

73 Following a single dose of 0.5 mg ibandronate by intravenous administration, patients  
74 with CL<sub>cr</sub> 40 to 70 mL/min had 55% higher exposure (AUC<sub>∞</sub>) than the exposure  
75 observed in subjects with CL<sub>cr</sub> >90 mL/min. Patients with CL<sub>cr</sub> <30 mL/min had more  
76 than a two-fold increase in exposure compared to the exposure for healthy subjects (see  
77 **DOSAGE AND ADMINISTRATION: Patients with Renal Impairment**).

78 **Hepatic Impairment**

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

81 **Drug Interactions**

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

86 **Melphalan/Prednisolone**

87 A pharmacokinetic interaction study in multiple myeloma patients demonstrated that  
88 intravenous melphalan (10 mg/m<sup>2</sup>) and oral prednisolone (60 mg/m<sup>2</sup>) did not interact with  
89 6 mg ibandronate upon intravenous coadministration. Ibandronate did not interact with  
90 melphalan or prednisolone.

91 **Tamoxifen**

92 A pharmacokinetic interaction study in healthy postmenopausal women demonstrated  
93 that there was no interaction between oral 30 mg tamoxifen and intravenous 2 mg  
94 ibandronate.

95 **Pharmacodynamics**

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

106 In studies of postmenopausal women, BONIVA Injection at doses of 0.5 mg to 3 mg  
107 produced biochemical changes indicative of inhibition of bone resorption, including  
108 decreases of biochemical markers of bone collagen degradation (cross-linked  
109 C-telopeptide of Type I collagen [CTX]). Changes in markers of bone formation  
110 (osteocalcin) were observed later than changes in resorption markers, as expected, due to  
111 the coupled nature of bone resorption and formation.

112 Year 1 results from an efficacy and safety study comparing BONIVA Injection 3 mg  
113 every 3 months and BONIVA 2.5 mg daily oral tablet demonstrated that both dosing  
114 regimens significantly suppressed serum CTX levels at Months 3, 6, and 12. The median  
115 pre-dose or trough serum CTX levels in the ITT population reached a nadir of 57%  
116 (BONIVA Injection) and 62% (BONIVA 2.5 mg tablets) below baseline values by  
117 Month 6, and remained stable at Month 12 of treatment.

## 118 **Clinical Studies**

### 119 **Daily Oral Tablets**

120 The effectiveness and safety of BONIVA daily oral tablets were demonstrated in a  
121 randomized, double-blind, placebo-controlled, multinational study (Treatment Study) of  
122 2946 women aged 55 to 80 years, who were on average 21 years postmenopause, who  
123 had lumbar spine bone mineral density (BMD) 2 to 5 SD below the premenopausal mean  
124 (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral  
125 fractures. BONIVA was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently.  
126 The main outcome measure was the occurrence of new radiographically diagnosed,  
127 vertebral fractures after 3 years of treatment. The diagnosis of an incident vertebral  
128 fracture was based on both qualitative diagnosis by the radiologist and quantitative  
129 morphometric criterion. The morphometric criterion required the dual occurrence of two  
130 events: a relative height ratio or relative height reduction in a vertebral body of at least  
131 20%, together with at least a 4 mm absolute decrease in height. All women received  
132 400 IU vitamin D and 500 mg calcium supplementation per day.

### 133 **Quarterly IV Injection**

134 The effectiveness and safety of BONIVA Injection 3 mg once every 3 months were  
135 demonstrated in a randomized, double-blind, multinational, noninferiority study (DIVA  
136 Study) in 1358 women with postmenopausal osteoporosis (L2-L4 lumbar spine BMD,  
137 T-score below -2.5 SD at baseline). The control group received BONIVA 2.5 mg daily  
138 oral tablets. The primary efficacy parameter was the relative change from baseline to 1  
139 year of treatment in lumbar spine BMD, which was compared between the intravenous  
140 injection and the daily oral treatment groups. All patients received 400 IU vitamin D and  
141 500 mg calcium supplementation per day.

### 142 **Effect on Vertebral Fracture**

143 BONIVA 2.5 mg daily oral tablet significantly reduced the incidence of new vertebral  
144 and of new and worsening vertebral fractures (Daily Oral Tablet – Treatment Study).  
145 Over the course of the 3-year study, the risk for vertebral fracture was 9.6% in the  
146 placebo-treated women and 4.7% in the women treated with BONIVA 2.5 mg daily oral

147 tablet (p<0.001) (see **Table 1**). In an unapproved regimen, intermittent oral  
 148 administration of 20 mg BONIVA, involving a 9- to 10-week drug-free interval,  
 149 produced a statistically significant reduction (50%) in the incidence of new vertebral  
 150 fractures, similar to that seen with the daily oral 2.5 mg regimen.

151 **Table 1**            **Effect of BONIVA Daily Oral Tablet on the Incidence of**  
 152                            **Vertebral Fracture in the 3-Year Osteoporosis Treatment**  
 153                            **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 0-3 Year	9.6	4.7	4.9 (2.3, 7.4)	52** (29, 68)
New and Worsening Vertebral Fracture 0-3 Year	10.4	5.1	5.3 (2.6, 7.9)	52 (30, 67)
Clinical (Symptomatic) Vertebral Fracture 0-3 Year	5.3	2.8	2.5 (0.6, 4.5)	49 (14, 69)

154 \*The endpoint value is the value at the study's last time point, 3 years, for all patients who had a fracture  
 155 identified at that time; otherwise, the last postbaseline value prior to the study's last time point is used.

156 \*\*p=0.0003 vs. placebo

157  
 158 **Effect on Nonvertebral Fractures**

159 There was a similar number of nonvertebral osteoporotic fractures at 3 years reported in  
 160 women treated with BONIVA 2.5 mg daily oral tablet [9.1%, (95% CI: 7.1%, 11.1%)]  
 161 and placebo [8.2%, (95% CI: 6.3%, 10.2%)]. The two treatment groups were also similar  
 162 with regard to the number of fractures reported at the individual non-vertebral sites:  
 163 pelvis, femur, wrist, forearm, rib, and hip (Daily Oral Tablet - Treatment Study).

164 **Effect on Bone Mineral Density (BMD)**

165 *Daily Oral Tablet - Treatment Study:* BONIVA 2.5 mg daily oral tablet significantly  
 166 increased BMD at the lumbar spine and hip relative to treatment with placebo. In the  
 167 3-year osteoporosis treatment study, BONIVA 2.5 mg daily oral tablet produced  
 168 increases in lumbar spine BMD that were progressive over 3 years of treatment and were  
 169 statistically significant relative to placebo at 6 months and at all later time points. Lumbar  
 170 spine BMD increased by 6.4% after 3 years of treatment with BONIVA 2.5 mg daily oral  
 171 tablet compared with 1.4% in the placebo group. Table 2 displays the significant

172 increases in BMD seen at the lumbar spine, total hip, femoral neck, and trochanter  
173 compared to placebo. Thus, overall BONIVA 2.5 mg daily oral tablet reverses the loss of  
174 BMD, a central factor in the progression of osteoporosis.

175 **Table 2**                    **Mean Percent Change in BMD from Baseline to Endpoint in**  
176 **Patients Treated with BONIVA 2.5 mg Daily Oral Tablet or**  
177 **Placebo in the 3-Year Osteoporosis Treatment Study\***

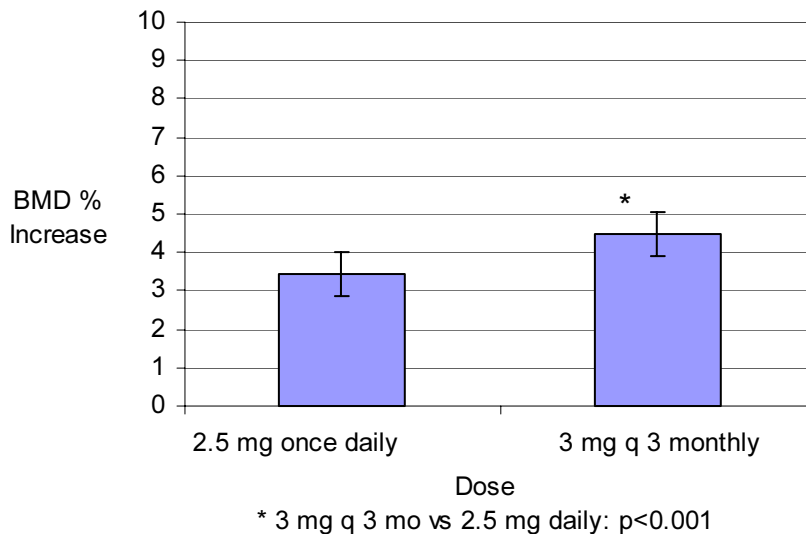
	<b>Placebo</b>	<b>BONIVA 2.5 mg</b>
Lumbar Spine	1.4 (n=693)	6.4 (n=712)
Total Hip	-0.7 (n=638)	3.1 (n=654)
Femoral Neck	-0.7 (n=683)	2.6 (n=699)
Trochanter	0.2 (n=683)	5.3 (n=699)

178 \*The endpoint value is the value at the study's last time point, 3 years,  
179 for all patients who had BMD measured at that time; otherwise the last  
180 postbaseline value prior to the study's last time point is used.

181 *Quarterly IV Injection – DIVA Study:* In the ITT efficacy analysis, the least-squares  
182 mean increase at 1 year in lumbar spine BMD in patients (n=429) treated with BONIVA  
183 Injection 3 mg once every 3 months (4.5%) was statistically superior to that in patients  
184 (n=434) treated with daily oral tablets (3.5%). The mean difference between groups was  
185 1.05% (95% CI: 0.53%, 1.57%; p<0.001; see **Figure 1**). The mean increases from  
186 baseline in total hip BMD at 1 year were 2.1% in the BONIVA Injection 3 mg once every  
187 3 months group and 1.5% in the BONIVA 2.5 mg daily oral tablet group. Consistently  
188 higher BMD increases at the femoral neck and trochanter were also observed following  
189 BONIVA Injection 3 mg once every 3 months compared to BONIVA 2.5 mg daily oral  
190 tablet.

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**Figure 1** Mean Percent Change (95% CI) from Baseline in Lumbar Spine BMD at One Year in Patients Treated with BONIVA 2.5 mg Daily Oral Tablet or BONIVA Injection 3 mg Once Every 3 Months



195

## 196 Bone Histology

197 The effects of BONIVA 2.5 mg daily oral tablet on bone histology were evaluated in iliac  
198 crest biopsies from 16 women after 22 months of treatment and 20 women after  
199 34 months of treatment. The histological analysis of bone biopsies showed bone of  
200 normal quality and no indication of osteomalacia or a mineralization defect.

201 The histological analysis of bone biopsies after 22 months of treatment with 3 mg  
202 intravenous ibandronate every 3 months (n=30) or 23 months of treatment with 2 mg  
203 intravenous ibandronate every 2 months (n=27) in women with postmenopausal  
204 osteoporosis showed bone of normal quality and no indication of a mineralization defect.

## 205 Animal Pharmacology

206 Animal studies have shown that ibandronate is an inhibitor of osteoclast-mediated bone  
207 resorption. In the Schenk assay in growing rats, ibandronate inhibited bone resorption and  
208 increased bone volume, based on histologic examination of the tibial metaphyses. There  
209 was no evidence of impaired mineralization at the highest dose of 5 mg/kg/day  
210 (subcutaneously), which is 1000 times the lowest antiresorptive dose of 0.005 mg/kg/day  
211 in this model, and 5000 times the optimal antiresorptive dose of 0.001 mg/kg/day in the  
212 aged ovariectomized rat. This indicates that BONIVA Injection administered at a  
213 therapeutic dose is unlikely to induce osteomalacia.

214 Long-term daily or intermittent administration of ibandronate to ovariectomized rats or  
215 monkeys was associated with suppression of bone turnover and increases in bone mass.  
216 Vertebral BMD, trabecular density, and biomechanical strength were increased  
217 dose-dependently in rats and monkeys, at doses up to 8 to 4 times the human intravenous

218 dose of 3 mg every 3 months, based on cumulative dose normalized for body surface area  
219 ( $\text{mg}/\text{m}^2$ ) and AUC comparison, respectively. Ibandronate maintained the positive  
220 correlation between bone mass and strength at the ulna and femoral neck. New bone  
221 formed in the presence of ibandronate had normal histologic structure and did not show  
222 mineralization defects.

## 223 **INDICATIONS AND USAGE**

224 BONIVA Injection is indicated for the treatment of osteoporosis in postmenopausal  
225 women.

226 In postmenopausal women with osteoporosis, BONIVA increases BMD and reduces the  
227 incidence of vertebral fractures (see **CLINICAL PHARMACOLOGY: Clinical**  
228 **Studies**). Osteoporosis may be confirmed by the presence or history of osteoporotic  
229 fracture or by a finding of low bone mass (BMD more than 2.0 standard deviations below  
230 the premenopausal mean [ie, T-score]).

## 231 **CONTRAINDICATIONS**

- 232 • Known hypersensitivity to BONIVA Injection or to any of its excipients
  - 233 • Uncorrected hypocalcemia (see **PRECAUTIONS: General**)
- 234

## 235 **WARNINGS**

236 BONIVA Injection, like other bisphosphonates administered intravenously, may cause a  
237 transient decrease in serum calcium values (see **PRECAUTIONS**).

238 BONIVA Injection must only be administered intravenously. Care must be taken not to  
239 administer BONIVA Injection intra-arterially or paravenously as this could lead to tissue  
240 damage.

241 Do not administer BONIVA Injection by any other route of administration. The safety  
242 and efficacy of BONIVA Injection following non-intravenous routes of administration  
243 have not been established.

## 244 **PRECAUTIONS**

### 245 **General**

#### 246 **Mineral Metabolism**

247 Hypocalcemia, hypovitaminosis D, and other disturbances of bone and mineral  
248 metabolism must be effectively treated before starting BONIVA Injection therapy.  
249 Adequate intake of calcium and vitamin D is important in all patients. Patients must  
250 receive supplemental calcium and vitamin D.

#### 251 **Renal Impairment**

252 Treatment with intravenous bisphosphonates has been associated with renal toxicity  
253 manifested as deterioration in renal function (ie, increased serum creatinine) and in rare  
254 cases, acute renal failure. No cases of acute renal failure were observed in controlled  
255 clinical trials in which intravenous BONIVA was administered as a 15- to 30-second

256 bolus. The risk of serious renal toxicity with other intravenous bisphosphonates appears  
257 to be inversely related to the rate of drug administration.

258 Patients who receive BONIVA Injection should have serum creatinine measured prior to  
259 each dosage administration. Patients with concomitant diseases that have the potential for  
260 adverse effects on the kidney or patients who are taking concomitant medications that  
261 have the potential for adverse effects on the kidney should be assessed, as clinically  
262 appropriate. Treatment should be withheld for renal deterioration.

263 BONIVA Injection should not be administered to patients with severe renal impairment  
264 (ie, patients with serum creatinine >200 µmol/L [2.3 mg/dL] or creatinine clearance  
265 [measured or estimated] <30 mL/min).

### 266 **Jaw Osteonecrosis**

267 Osteonecrosis, primarily in the jaw, has been reported in patients treated with  
268 bisphosphonates. Most cases have been in cancer patients undergoing dental procedures,  
269 but some have occurred in patients with postmenopausal osteoporosis or other diagnoses.  
270 Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies  
271 (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, anemia,  
272 coagulopathy, infection, pre-existing dental disease). Most reported cases have been in  
273 patients treated with bisphosphonates intravenously but some have been in patients  
274 treated orally.

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

### 281 **Musculoskeletal Pain**

282 In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or  
283 muscle pain has been reported in patients taking bisphosphonates that are approved for  
284 the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS**). However,  
285 such reports have been infrequent. This category of drugs includes BONIVA  
286 (ibandronate sodium) Injection. Most of the patients were postmenopausal women. The  
287 time to onset of symptoms varied from one day to several months after starting the drug.  
288 Most patients had relief of symptoms after stopping. A subset had recurrence of  
289 symptoms when rechallenged with the same drug or another bisphosphonate.

### 290 **Information for Patients**

291 BONIVA Injection must be administered intravenously only by a health care  
292 professional. Patients should be instructed to read the Patient Information Leaflet  
293 carefully before BONIVA Injection is administered and to re-read it each time the  
294 prescription is renewed.

295 BONIVA Injection should be administered once every 3 months. If the dose is missed,  
296 the injection should be administered as soon as it can be rescheduled. Thereafter,  
297 injections should be scheduled every 3 months from the date of the last injection. Do not  
298 administer BONIVA Injection more frequently than once every 3 months.

299 Patients must receive supplemental calcium and vitamin D.

## 300 **Drug Interactions**

301 See **CLINICAL PHARMACOLOGY: Drug Interactions**

## 302 **Drug/Laboratory Test Interactions**

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

## 305 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

### 306 **Carcinogenesis**

307 In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered  
308 by oral gavage to Wistar rats (systemic exposures in males and females up to 3 and 1  
309 times, respectively, human exposure at the recommended intravenous dose of 3 mg every  
310 3 months, based on cumulative AUC comparison). There were no significant drug-related  
311 tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20,  
312 or 40 mg/kg/day were administered by oral gavage to NMRI mice (exposures in males  
313 and females up to 96 and 14 times, respectively, human exposure at the recommended  
314 intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). There  
315 were no significant drug-related tumor findings in male or female mice. In a 90-week  
316 carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking  
317 water to NMRI mice. A dose-related increased incidence of adrenal subcapsular  
318 adenoma/carcinoma was observed in female mice, which was statistically significant at  
319 80 mg/kg/day (32 to 51 times human exposure at the recommended intravenous dose of  
320 3 mg every 3 months, based on cumulative AUC comparison). The relevance of these  
321 findings to humans is unknown.

### 322 **Mutagenesis**

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

### 329 **Impairment of Fertility**

330 In female rats treated from 14 days prior to mating through gestation, decreases in  
331 fertility, corpora lutea and implantation sites, and increased preimplantation loss were  
332 observed at an intravenous dose of 1.2 mg/kg/day (117 times human exposure at the  
333 recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC

334 comparison). In male rats treated for 28 days prior to mating, a decrease in sperm  
335 production and altered sperm morphology were observed at intravenous doses  $\geq 0.3$   
336 mg/kg/day ( $\geq 40$  times human exposure at the recommended intravenous dose of 3 mg  
337 every 3 months, based on cumulative AUC comparison).

## 338 **Pregnancy**

### 339 **Pregnancy Category C**

340 In pregnant rats given intravenous doses of 0.05, 0.15, or 0.5 mg/kg/day from Day 17  
341 post-coitum until Day 20 post-partum, ibandronate treatment resulted in dystocia,  
342 maternal mortality, and early postnatal pup loss in all dose groups ( $\geq 2$  times human  
343 exposure at the recommended intravenous dose of 3 mg every 3 months, based on  
344 cumulative AUC comparison). Reduced body weight at birth was observed at 0.15 and  
345 0.5 mg/kg/day ( $\geq 4$  times human exposure at the recommended intravenous dose of 3 mg  
346 every 3 months, based on cumulative AUC comparison). Pups exhibited abnormal  
347 odontogeny that decreased food consumption and body weight gain at 0.15 and 0.5  
348 mg/kg/day ( $\geq 18$  times human exposure at the recommended intravenous dose of 3 mg  
349 every 3 months, based on cumulative AUC comparison). Periparturient mortality has also  
350 been observed with other bisphosphonates and appears to be a class effect related to  
351 inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia.

352 Exposure of pregnant rats during the period of organogenesis resulted in an increased  
353 fetal incidence of RPU (renal pelvis ureter) syndrome at an intravenous dose of  
354 1 mg/kg/day ( $\geq 47$  times human exposure at the recommended intravenous dose of 3 mg  
355 every 3 months, based on cumulative AUC comparison). In this spontaneous delivery  
356 study, dystocia was counteracted by perinatal calcium supplementation. In rat studies  
357 with intravenous dosing during gestation, fetal weight and pup growth were reduced at  
358 doses  $\geq 0.1$  mg/kg/day ( $\geq 5$  times human exposure at the recommended intravenous dose  
359 of 3 mg every 3 months, based on cumulative AUC comparison).

360 In pregnant rabbits given intravenous doses of 0.03, 0.07 or 0.2 mg/kg/day during the  
361 period of organogenesis, maternal mortality, reduced maternal body weight gain,  
362 decreased litter size due to increased resorption rate, and decreased fetal weight were  
363 observed at 0.2 mg/kg/day (19 times the recommended human intravenous dose of 3 mg  
364 every 3 months, based on cumulative body surface area comparison,  $\text{mg}/\text{m}^2$ ).

365 Bisphosphonates are incorporated into the bone matrix, from where they are gradually  
366 released over periods of weeks to years. The extent of bisphosphonate incorporation into  
367 adult bone, and hence, the amount available for release back into the systemic circulation,  
368 is directly related to the total dose and duration of bisphosphonate use. Although there are  
369 no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and  
370 animal data suggest that uptake of bisphosphonates into fetal bone is greater than into  
371 maternal bone. Therefore, there is a theoretical risk of fetal harm (eg, skeletal and other  
372 abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate  
373 therapy. The impact of variables such as time between cessation of bisphosphonate  
374 therapy to conception, the particular bisphosphonate used, and the route of administration  
375 (intravenous versus oral) on this risk has not been established.

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

### 379 **Nursing Mothers**

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

### 386 **Pediatric Use**

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

### 388 **Geriatric Use**

389 Of the patients receiving BONIVA Injection 3 mg every 3 months for 1 year (DIVA  
390 study), 51% were over 65 years of age. No overall differences in effectiveness or safety  
391 were observed between these patients and younger patients, but greater sensitivity in  
392 some older individuals cannot be ruled out.

## 393 **ADVERSE REACTIONS**

### 394 **Daily Oral Tablet**

395 Treatment with BONIVA 2.5 mg daily oral tablet was studied in over 3900 patients in  
396 postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event  
397 profile of BONIVA 2.5 mg once daily tablet in these studies was similar to that of  
398 placebo.

399 Most adverse events were mild or moderate and did not lead to discontinuation. The  
400 incidence of serious adverse events was 20% in the placebo group and 23% in the  
401 BONIVA 2.5 mg daily oral tablet group. The percentage of patients who withdrew from  
402 treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg  
403 daily oral tablet group and the placebo group. Overall, and according to body system,  
404 there was no difference between BONIVA daily oral tablet and placebo, with adverse  
405 events of the digestive system being the most common reason for withdrawal.

406 Table 3 lists adverse events from the Treatment and Prevention Studies reported in  $\geq 2\%$   
407 of patients and in more patients treated with BONIVA 2.5 mg daily oral tablet than  
408 patients treated with placebo. Adverse events are shown without attribution of causality.

409 **Table 3** Adverse Events Occurring at a Frequency  $\geq 2\%$  and in More  
 410 Patients Treated with BONIVA 2.5 mg Daily Oral Tablet than  
 411 in Patients Treated with Placebo in the Osteoporosis  
 412 Treatment and Prevention Studies

Body System	Placebo % (n=1134)	BONIVA 2.5 mg daily % (n=1140)
<b>Body as a Whole</b>		
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
<b>Digestive System</b>		
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
<b>Metabolic and Nutritional Disorders</b>		
Hypercholesterolemia	4.2	4.8
<b>Musculoskeletal System</b>		
Myalgia	5.1	5.7
Joint Disorder	3.3	3.6
Arthritis	2.7	3.2
<b>Nervous System</b>		
Headache	5.8	6.5
Dizziness	2.6	3.7
Vertigo	2.5	3.0
Nerve Root Lesion	1.9	2.2
<b>Respiratory System</b>		
Upper Respiratory Infection	33.2	33.7
Bronchitis	6.8	10.0
Pneumonia	4.3	5.9
Pharyngitis	1.5	2.5
<b>Urogenital System</b>		
Urinary Tract Infection	4.2	5.5

413

414 **Quarterly IV Injection – DIVA Study**

415 In a 1-year, double-blind, multicenter study comparing BONIVA Injection administered  
 416 intravenously as 3 mg every 3 months to BONIVA 2.5 mg daily oral tablet in women  
 417 with postmenopausal osteoporosis, the overall safety and tolerability profiles of the two

418 dosing regimens were similar. The incidence of serious adverse events was 8.0% in the  
 419 BONIVA 2.5 mg daily group and 7.5% in the BONIVA Injection 3 mg once every 3  
 420 months group. The percentage of patients who withdrew from treatment due to adverse  
 421 events was approximately 6.7% in the BONIVA 2.5 mg daily group and 8.5% in the  
 422 BONIVA Injection 3 mg every 3 months group.

423 Table 4 lists the adverse events reported in >2% of patients without attribution of  
 424 causality.

425 **Table 4** Adverse Events With an Incidence of at Least 2% in Patients  
 426 Treated with BONIVA Injection (3 mg once every 3 months)  
 427 or BONIVA Daily Oral Tablet (2.5 mg)

Body System/Adverse Event	BONIVA 2.5 mg Daily (Oral) % (n=465)	BONIVA 3 mg q 3 mo (IV) % (n=469)
<b>Infections and Infestations</b>		
Influenza	8.0	4.7
Nasopharyngitis	6.0	3.4
Cystitis	3.4	1.9
Gastroenteritis	3.4	1.5
Urinary Tract Infection	3.2	2.6
Bronchitis	2.8	2.1
Upper Respiratory Tract Infection	2.8	1.1
<b>Gastrointestinal Disorders</b>		
Abdominal Pain*	5.6	5.1
Dyspepsia	4.3	3.6
Nausea	4.3	2.1
Constipation	4.1	3.4
Diarrhea	2.4	2.8
Gastritis	2.2	1.9
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	8.6	9.6
Back Pain	7.5	7.0
Localized Osteoarthritis	2.4	1.5
Pain in Extremity	2.2	2.8
Myalgia	0.9	2.8
<b>Nervous System Disorders</b>		
Dizziness	2.8	1.9
Headache	2.6	3.6
<b>Vascular Disorders</b>		
Hypertension	7.1	5.3
<b>Psychiatric Disorders</b>		
Insomnia	2.6	1.1

Depression	2.2	1.3
<b>General Disorders and Administration Site Conditions</b>		
Influenza-like Illness†	1.1	4.9
Fatigue	1.1	2.8
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash‡	2.8	2.3
<b>Metabolism and Nutrition Disorders</b>		
Hypercholesterolemia	4.3	1.5

428 \* Is a combination of abdominal pain and abdominal pain upper

429 † Combination of influenza-like illness and acute phase reaction

430 ‡ Combination of rash, rash pruritic, rash macular, dermatitis, dermatitis allergic, exanthem, erythema, rash  
431 papular, rash generalized, dermatitis medicamentosa, rash erythematous

#### 432 Acute Phase Reaction-like Events

433 Symptoms consistent with acute phase reaction (APR) have been reported with  
434 intravenous bisphosphonate use. The overall incidence of patients with APR-like events  
435 was higher in the intravenous treatment group (4% in the BONIVA 2.5 mg daily oral  
436 tablet group vs. 10% in the BONIVA Injection 3 mg once every 3 months group). These  
437 incidence rates are based on reporting of any of 33 potential APR-like symptoms within 3  
438 days of an IV dose and for a duration of 7 days or less. In most cases, no specific  
439 treatment was required and the symptoms subsided within 24 to 48 hours.

#### 440 Injection Site Reactions

441 Local reactions at the injection site, such as redness or swelling, were observed  
442 infrequently, but at a higher incidence in patients treated with BONIVA Injection 3 mg  
443 every 3 months (<2%; 8/469) than in patients treated with placebo injections (<1%;  
444 1/465). In most cases, the reaction was of mild to moderate severity.

#### 445 Ocular Adverse Events

446 Bisphosphonates may be associated with ocular inflammation such as uveitis and  
447 scleritis. In some cases, these events did not resolve until the bisphosphonate was  
448 discontinued.

#### 449 Laboratory Test Findings

450 There were no clinically significant changes from baseline values or shifts in any  
451 laboratory variable with oral ibandronate. As expected with bisphosphonate treatment, a  
452 decrease in total alkaline phosphatase levels was seen with 2.5 mg daily oral ibandronate  
453 compared to placebo. There was no difference compared with placebo for laboratory  
454 abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or  
455 hypophosphatemia. There also was no evidence that BONIVA Injection 3 mg every 3  
456 months induced clinically significant laboratory abnormalities indicative of hepatic or  
457 renal dysfunction compared to BONIVA 2.5 mg daily oral tablet.

458 **OVERDOSAGE**

459 No cases of overdose were reported in premarketing studies with BONIVA Injection.  
460 Intravenous overdose may result in hypocalcemia, hypophosphatemia, and  
461 hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus,  
462 and magnesium should be corrected by intravenous administration of calcium gluconate,  
463 potassium or sodium phosphate, and magnesium sulfate, respectively.

464 Dialysis would not be beneficial unless it is administered within 2 hours following the  
465 overdose.

466 **DOSAGE AND ADMINISTRATION**

467 The recommended dose of BONIVA Injection for the treatment of postmenopausal  
468 osteoporosis is 3 mg every 3 months (see **INDICATIONS AND USAGE**) administered  
469 over a period of 15 to 30 seconds.

470 No cases of acute renal failure were observed in controlled clinical trials in which  
471 intravenous BONIVA was administered as a 15- to 30-second bolus. The risk of serious  
472 renal toxicity with other intravenous bisphosphonates appears to be inversely related to  
473 the rate of drug administration (see **PRECAUTIONS**).

474 BONIVA Injection must be administered by a health care professional.

475 BONIVA Injection must only be administered intravenously (see **WARNINGS**). Care  
476 must be taken not to administer BONIVA Injection intra-arterially or paravenously as this  
477 could lead to tissue damage.

478 Do not administer BONIVA Injection by any other route of administration. The safety  
479 and efficacy of BONIVA Injection following non-intravenous routes of administration  
480 have not been established.

481 Administer BONIVA Injection using the enclosed needle. Prefilled syringes are for single  
482 use only. Discard unused portion.

483 BONIVA Injection must not be mixed with calcium-containing solutions or other  
484 intravenously administered drugs.

485 Parenteral drug products should be inspected visually for particulate matter and  
486 discoloration before administration, and not used if particulate matter is visible or product  
487 is discolored. Prefilled syringes with particulate matter or discoloration should not be  
488 used.

489 If the dose is missed, BONIVA Injection should be administered as soon as it can be  
490 rescheduled. Thereafter, injections should be scheduled every 3 months from the date of  
491 the last injection. Do not administer BONIVA Injection (3 mg) more frequently than once  
492 every 3 months.

493 Patients must receive supplemental calcium and vitamin D (see **PRECAUTIONS:**  
494 **Information for Patients**).

495 **Patients with Hepatic Impairment**

496 No dose adjustment is necessary (see **CLINICAL PHARMACOLOGY: Special**  
497 **Populations**).

498 **Patients with Renal Impairment**

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

501 BONIVA Injection should not be administered to patients with severe renal impairment,  
502 ie, patients with serum creatinine >200 µmol/L (2.3 mg/dL) or creatinine clearance  
503 (measured or estimated) <30 mL/min (see **CLINICAL PHARMACOLOGY: Special**  
504 **Populations**).

505 **Geriatric Patients**

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

507 **HOW SUPPLIED**

508 One prefilled syringe of BONIVA Injection (ibandronate sodium), 3 mg/3 mL single-use,  
509 clear glass prefilled syringe, in a box with 1 needle and 2 alcohol swabs  
510 (NDC 0004-0188-09).

511 Each syringe is a 5 mL (5 cc) volume syringe supplied with a 23-gauge, 3/4 inch needle  
512 with needle-stick protection device.

513 **Storage**

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

516

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