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APPLICATION NUMBER:

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LABELING



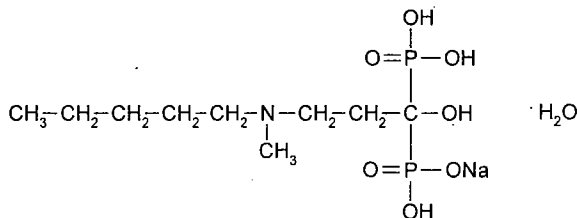
BONIVA[®]
(ibandronate sodium)
INJECTION

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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 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 maximum
36 serum ibandronate concentrations upon intravenous bolus administration) in one study.

37 Metabolism

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

40 Elimination

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

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

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

57 Special Populations

58 Pediatrics

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

60 Gender

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

62 Geriatric

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

67 **Race**

68 Pharmacokinetic differences due to race have not been studied.

69 **Renal Impairment**

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

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

77 **Hepatic Impairment**

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

80 **Drug Interactions**

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

85 **Melphalan/Prednisolone**

86 A pharmacokinetic interaction study in multiple myeloma patients demonstrated that
87 intravenous melphalan (10 mg/m²) and oral prednisolone (60 mg/m²) did not interact with
88 6 mg ibandronate upon intravenous coadministration. Ibandronate did not interact with
89 melphalan or prednisolone.

90 **Tamoxifen**

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

94 **Pharmacodynamics**

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

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

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

117 **Clinical Studies**

118 **Daily Oral Tablets**

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

132 **Quarterly IV Injection**

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

141 **Effect on Vertebral Fracture**

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

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

150 **Table 1** **Effect of BONIVA Daily Oral Tablet on the Incidence of**
 151 **Vertebral Fracture in the 3-Year Osteoporosis Treatment**
 152 **Study***

	Proportion of Patients with Fracture (%)		Absolute Risk	Relative Risk
	Placebo n=975	BONIVA 2.5 mg daily n=977	Reduction (%) 95% CI	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)

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

155 **p=0.0003 vs. placebo

156

157 **Effect on Nonvertebral Fractures**

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

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

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

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

	Placebo	BONIVA 2.5 mg
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)

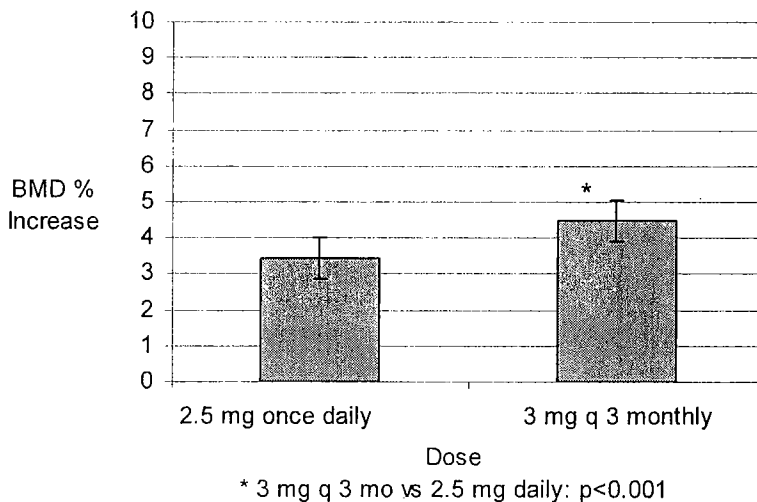
*The endpoint value is the value at the study's last time point, 3 years, for all patients who had BMD measured at that time; otherwise the last post-baseline value prior to the study's last time point is used.

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

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

193



194

195 **Bone Histology**

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

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

204 **Animal Pharmacology**

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

213 Long-term daily or intermittent administration of ibandronate to ovariectomized rats or
214 monkeys was associated with suppression of bone turnover and increases in bone mass.
215 Vertebral BMD, trabecular density, and biomechanical strength were increased
216 dose-dependently in rats and monkeys, at doses up to 8 to 4 times the human intravenous
217 dose of 3 mg every 3 months, based on cumulative dose normalized for body surface area
218 (mg/m^2) and AUC comparison, respectively. Ibandronate maintained the positive
219 correlation between bone mass and strength at the ulna and femoral neck. New bone
220 formed in the presence of ibandronate had normal histologic structure and did not show
221 mineralization defects.

222 **INDICATIONS AND USAGE**

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

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

230 **CONTRAINDICATIONS**

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

234 **WARNINGS**

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

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

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

243 **PRECAUTIONS**

244 **General**

245 **Mineral Metabolism**

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

250 **Renal Impairment**

251 Treatment with intravenous bisphosphonates has been associated with renal toxicity
252 manifested as deterioration in renal function (ie, increased serum creatinine) and in rare
253 cases, acute renal failure. No cases of acute renal failure were observed in controlled
254 clinical trials in which intravenous BONIVA was administered as a 15- to 30-second
255 bolus. The risk of serious renal toxicity with other intravenous bisphosphonates appears
256 to be inversely related to the rate of drug administration.

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

262 BONIVA Injection should not be administered to patients with severe renal impairment
263 (ie, patients with serum creatinine >200 $\mu\text{mol/L}$ [2.3 mg/dL] or creatinine clearance
264 [measured or estimated] <30 mL/min).

265 **Jaw Osteonecrosis**

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

272 patients treated with bisphosphonates intravenously but some have been in patients
273 treated orally.

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

280 **Information for Patients**

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

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

289 Patients must receive supplemental calcium and vitamin D.

290 **Drug Interactions**

291 See **CLINICAL PHARMACOLOGY: Drug Interactions**

292 **Drug/Laboratory Test Interactions**

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

295 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

296 **Carcinogenesis**

297 In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered
298 by oral gavage to Wistar rats (systemic exposures in males and females up to 3 and 1
299 times, respectively, human exposure at the recommended intravenous dose of 3 mg every
300 3 months, based on cumulative AUC comparison). There were no significant drug-related
301 tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20,
302 or 40 mg/kg/day were administered by oral gavage to NMRI mice (exposures in males
303 and females up to 96 and 14 times, respectively, human exposure at the recommended
304 intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). There
305 were no significant drug-related tumor findings in male or female mice. In a 90-week
306 carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking
307 water to NMRI mice. A dose-related increased incidence of adrenal subcapsular
308 adenoma/carcinoma was observed in female mice, which was statistically significant at
309 80 mg/kg/day (32 to 51 times human exposure at the recommended intravenous dose of

310 3 mg every 3 months, based on cumulative AUC comparison). The relevance of these
311 findings to humans is unknown.

312 Mutagenesis

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

319 Impairment of Fertility

320 In female rats treated from 14 days prior to mating through gestation, decreases in
321 fertility, corpora lutea and implantation sites, and increased preimplantation loss were
322 observed at an intravenous dose of 1.2 mg/kg/day (117 times human exposure at the
323 recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC
324 comparison). In male rats treated for 28 days prior to mating, a decrease in sperm
325 production and altered sperm morphology were observed at intravenous doses ≥ 0.3
326 mg/kg/day (≥ 40 times human exposure at the recommended intravenous dose of 3 mg
327 every 3 months, based on cumulative AUC comparison).

328 Pregnancy

329 Pregnancy Category C

330 In pregnant rats given intravenous doses of 0.05, 0.15, or 0.5 mg/kg/day from Day 17
331 post-coitum until Day 20 post-partum, ibandronate treatment resulted in dystocia,
332 maternal mortality, and early postnatal pup loss in all dose groups (≥ 2 times human
333 exposure at the recommended intravenous dose of 3 mg every 3 months, based on
334 cumulative AUC comparison). Reduced body weight at birth was observed at 0.15 and
335 0.5 mg/kg/day (≥ 4 times human exposure at the recommended intravenous dose of 3 mg
336 every 3 months, based on cumulative AUC comparison). Pups exhibited abnormal
337 odontogeny that decreased food consumption and body weight gain at 0.15 and 0.5
338 mg/kg/day (≥ 18 times human exposure at the recommended intravenous dose of 3 mg
339 every 3 months, based on cumulative AUC comparison). Periparturient mortality has also
340 been observed with other bisphosphonates and appears to be a class effect related to
341 inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia.

342 Exposure of pregnant rats during the period of organogenesis resulted in an increased
343 fetal incidence of RPU (renal pelvis ureter) syndrome at an intravenous dose of
344 1 mg/kg/day (≥ 47 times human exposure at the recommended intravenous dose of 3 mg
345 every 3 months, based on cumulative AUC comparison). In this spontaneous delivery
346 study, dystocia was counteracted by perinatal calcium supplementation. In rat studies
347 with intravenous dosing during gestation, fetal weight and pup growth were reduced at
348 doses ≥ 0.1 mg/kg/day (≥ 5 times human exposure at the recommended intravenous dose
349 of 3 mg every 3 months, based on cumulative AUC comparison).

350 In pregnant rabbits given intravenous doses of 0.03, 0.07 or 0.2 mg/kg/day during the
351 period of organogenesis, maternal mortality, reduce maternal body weight gain,
352 decreased litter size due to increased resorption rate, and decreased fetal weight were
353 observed at 0.2 mg/kg/day (19 times the recommended human intravenous dose of 3 mg
354 every 3 months, based on cumulative body surface area comparison, mg/m²).

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

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

369 **Nursing Mothers**

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

376 **Pediatric Use**

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

378 **Geriatric Use**

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

383 **ADVERSE REACTIONS**

384 **Daily Oral Tablet**

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

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

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

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

Body System	Placebo % (n=1134)	BONIVA 2.5 mg daily % (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

403

404 **Quarterly IV Injection – DIVA Study**

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

408 dosing regimens were similar. The incidence of serious adverse events was 8.0% in the
 409 BONIVA 2.5 mg daily group and 7.5% in the Injection 3 mg every 3 month group. The
 410 percentage of patients who withdrew from treatment due to adverse events was
 411 approximately 6.7% in the BONIVA 2.5 mg daily group and 8.5% in the BONIVA
 412 Injection 3 mg every 3 month group.

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

415 **Table 4 Adverse Events With an Incidence of at Least 2% in Patients**
 416 **Treated with BONIVA Injection (3 mg every 3 months) or**
 417 **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)
Infections and Infestations		
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
Gastrointestinal Disorders		
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
Musculoskeletal and Connective Tissue Disorders		
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
Nervous System Disorders		
Dizziness	2.8	1.9
Headache	2.6	3.6
Vascular Disorders		
Hypertension	7.1	5.3
Psychiatric Disorders		
Insomnia	2.6	1.1

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

418 * Is a combination of abdominal pain and abdominal pain upper

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

420 ‡ Combination of rash, rash pruritic, rash macular, dermatitis, dermatitis allergic, exanthem, erythema, rash
421 papular, rash generalized, dermatitis medicamentosa, rash erythematous

422 Acute Phase Reaction-like Events

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

430 Injection Site Reactions

431 Local reactions at the injection site, such as redness or swelling, were observed
432 infrequently, but at a higher incidence in patients treated with BONIVA Injection 3 mg
433 every 3 months (<2%; 8/469) than in patients treated with placebo injections (<1%;
434 1/465). In most cases, the reaction was of mild to moderate severity.

435 Ocular Adverse Events

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

439 Laboratory Test Findings

440 There were no clinically significant changes from baseline values or shifts in any
441 laboratory variable with oral ibandronate. As expected with bisphosphonate treatment, a
442 decrease in total alkaline phosphatase levels was seen with 2.5 mg daily oral ibandronate
443 compared to placebo. There was no difference compared with placebo for laboratory
444 abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or
445 hypophosphatemia. There also was no evidence that BONIVA Injection 3 mg every 3
446 months induced clinically significant laboratory abnormalities indicative of hepatic or
447 renal dysfunction compared to BONIVA 2.5 mg daily oral tablet.

448 **OVERDOSAGE**

449 No cases of overdose were reported in pre-marketing studies with BONIVA Injection.
450 Intravenous overdose may result in hypocalcemia, hypophosphatemia, and
451 hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus,
452 and magnesium should be corrected by intravenous administration of calcium gluconate,
453 potassium or sodium phosphate, and magnesium sulfate, respectively.

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

456 **DOSAGE AND ADMINISTRATION**

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

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

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

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

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

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

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

475 Parenteral drug products should be inspected visually for particulate matter and
476 discoloration before administration, and not used if particulate matter is visible or product
477 is discolored. Prefilled syringes with particulate matter or discoloration should not be
478 used.

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

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

485 **Patients with Hepatic Impairment**

486 No dose adjustment is necessary (see **CLINICAL PHARMACOLOGY: Special**
487 **Populations**).

488 **Patients with Renal Impairment**

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

491 BONIVA Injection should not be administered to patients with severe renal impairment,
492 ie, patients with serum creatinine >200 $\mu\text{mol/L}$ (2.3 mg/dL) or creatinine clearance
493 (measured or estimated) <30 mL/min (see **CLINICAL PHARMACOLOGY: Special**
494 **Populations**).

495 **Geriatric Patients**

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

497 **HOW SUPPLIED**

498 One prefilled syringe of BONIVA Injection (ibandronate sodium), 3 mg/3 mL single-use,
499 clear glass prefilled syringe, in a box with 1 needle and 1 alcohol swab
500 (NDC 0004-0188-09).

501 Each syringe is a 5 mL (5 cc) volume syringe supplied with a 23 gauge, 1 inch needle
502 with needle-stick protection device.

503 **Storage**

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

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Patient Information

BONIVA™ [bon-EE-va] (ibandronate sodium) INJECTION

R_x only

Read this patient information carefully before you receive BONIVA Injection. Read this patient information each time you get a refill for BONIVA Injection. There may be new information. This information does not take the place of talking with your health care provider about your condition or your treatment. Talk about BONIVA Injection with your health care provider before the first injection and at your regular check-ups.

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

BONIVA Injection must be administered intravenously only by a health care professional. **Do NOT administer BONIVA Injection to yourself.**

Patients with severe kidney problems should not receive BONIVA Injection.

Low blood calcium levels must be corrected before starting BONIVA Injection therapy. You also must take calcium and vitamin D supplements while receiving BONIVA Injection therapy.

What is BONIVA Injection?

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

BONIVA Injection may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who receive the injection, even though they won't be able to see or feel a difference. BONIVA Injection may help lower the chances of breaking bones (fractures). These effects continue as long as you receive BONIVA Injection.

It is important that you receive your BONIVA Injection every 3 months for as long as your health care provider prescribes it. BONIVA Injection can treat your osteoporosis only if you continue to receive treatment.

Who should not receive BONIVA Injection?

Do not begin treatment with BONIVA Injection if you:

- have low blood calcium (hypocalcemia) or low blood vitamin D (hypovitaminosis D)
- have kidneys that work very poorly

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

Tell your health care provider before using BONIVA Injection:

- if you are pregnant or planning to become pregnant. It is not known if BONIVA Injection can harm your unborn baby.
- if you are breast-feeding. It is not known if BONIVA Injection passes into your milk and if it can harm your baby.
- if you have kidney problems or other diseases that may affect your kidneys, such as diabetes, high blood pressure, or heart disease.
- **about all the medicines you take**, including prescription and non-prescription medicines, vitamins and supplements.

What is my BONIVA Injection schedule?

BONIVA Injection must be administered intravenously only by a health care professional. BONIVA Injection should be administered once every 3 months. If the dose is missed, you should contact your health care provider to schedule the next injection and to continue your treatment with BONIVA Injection. After receiving your missed dose, your next injection should be scheduled 3 months from the date of the last injection. If you are not sure what to do if you miss a dose, contact your health care provider who will be able to advise you.

What are the possible side effects of BONIVA Injection?

BONIVA Injection is generally well tolerated. Side effects with BONIVA Injection are usually mild and of brief duration.

Common side effects with BONIVA Injection are:

- bone, muscle, or joint pains
- influenza-like illness
- headache

You may experience flu-like symptoms consisting of fever, chills, joint, bone and/or muscle pain, and fatigue. These symptoms usually occur only after the first injection and generally will not happen again as you continue treatment. Your health care provider or pharmacist can recommend a mild pain reliever such as aspirin to make you more comfortable. Without treatment, the symptoms generally disappear within 24 to 48 hours.

You may experience irritation at the site of injection, such as redness or swelling, but this does not happen often.

These are not all the possible side effects of BONIVA Injection. For more information, ask your health care provider or pharmacist.

What is osteoporosis?

Osteoporosis is a disease that causes bones to become thinner. Thin bones can break easily. Most people think of their bones as being solid like a rock. Actually, bone is living

tissue, just like other parts of the body, such as your heart, brain, or skin. Bone just happens to be a harder type of tissue. Bone is always changing. Your body keeps your bones strong and healthy by replacing old bone with new bone.

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

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

Who is at risk for osteoporosis?

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

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

Women who:

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

People who:

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

General information about BONIVA Injection

Medicines are sometimes prescribed for conditions that are not mentioned in patient information. Do not use BONIVA Injection for a condition for which it was not prescribed.

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

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

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

For more information about BONIVA Injection, call 1-800-xxx-xxxx or visit www.xxxxxxxx.com.

What are the ingredients of BONIVA Injection?

BONIVA Injection (active ingredient): ibandronate sodium

BONIVA Injection (inactive ingredients): sodium chloride, glacial acetic acid, sodium acetate and water

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