Area under the serum ibandronate concentrations versus time curve increases in a dose- dependent manner. Ibandronate sodium has the following structural formula:

\[
\text{N}^\text{2} - \text{pentyl})\text{amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt,}
\]

BONIVA Injection is intended for intravenous administration only. BONIVA Injection is available in a single-use vial containing 2.5 mg of ibandronate monosodium salt monohydrate in 3 mL of solution, equivalent to 2.25 mg of ibandronate free acid. Inactive ingredients include sodium chloride, glacial acetic acid, and water for injection. BONIVA Injection is a clear, colorless solution. PLASMA ELIMINATION: The plasma elimination of ibandronate is multiphasic. Its renal clearance and distribution volume are dose dependent and increase in direct proportion to the dose. Ibandronate sodium has the following structural formula:

\[
\text{C}_9\text{H}_{22}\text{NO}_7\text{P}_2\text{Na}_2
\]

CLINICAL PHARMACOLOGY: The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which underlies its antiresorptive effect. Ibandronate is a pyrophosphate with the chemical name for ibandronate sodium is 3-(N2-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt.

Mechanism of Action: The bone reabsorption and resorption phase are coupled processes. During bone resorption, osteoclasts release matrix metalloproteinases that degrade the organic and inorganic components of bone matrix, resulting in bone loss and increased risk of fracture. After menopause, the risk of fractures increases due to the coupled nature of bone remodeling, leading to bone loss and increased risk of fracture. Ibandronate is a pyrophosphate with the chemical name for ibandronate sodium is 3-(N2-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt.

The plasma elimination of ibandronate is multiphasic. Its renal clearance and distribution volume are dose dependent and increase in direct proportion to the dose. Ibandronate sodium has the following structural formula:

\[
\text{C}_9\text{H}_{22}\text{NO}_7\text{P}_2\text{Na}_2
\]

CLINICAL PHARMACOLOGY: The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which underlies its antiresorptive effect. Ibandronate is a pyrophosphate with the chemical name for ibandronate sodium is 3-(N2-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt.

Mechanism of Action: The bone reabsorption and resorption phase are coupled processes. During bone resorption, osteoclasts release matrix metalloproteinases that degrade the organic and inorganic components of bone matrix, resulting in bone loss and increased risk of fracture. After menopause, the risk of fractures increases due to the coupled nature of bone remodeling, leading to bone loss and increased risk of fracture.

Ibandronate sodium is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents. Ibandronate sodium has the following structural formula:

\[
\text{C}_9\text{H}_{22}\text{NO}_7\text{P}_2\text{Na}_2
\]

CLINICAL PHARMACOLOGY: The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which underlies its antiresorptive effect. Ibandronate is a pyrophosphate with the chemical name for ibandronate sodium is 3-(N2-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt.

Mechanism of Action: The bone reabsorption and resorption phase are coupled processes. During bone resorption, osteoclasts release matrix metalloproteinases that degrade the organic and inorganic components of bone matrix, resulting in bone loss and increased risk of fracture. After menopause, the risk of fractures increases due to the coupled nature of bone remodeling, leading to bone loss and increased risk of fracture.

Ibandronate sodium is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents. Ibandronate sodium has the following structural formula:

\[
\text{C}_9\text{H}_{22}\text{NO}_7\text{P}_2\text{Na}_2
\]

CLINICAL PHARMACOLOGY: The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which underlies its antiresorptive effect. Ibandronate is a pyrophosphate with the chemical name for ibandronate sodium is 3-(N2-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt.

Mechanism of Action: The bone reabsorption and resorption phase are coupled processes. During bone resorption, osteoclasts release matrix metalloproteinases that degrade the organic and inorganic components of bone matrix, resulting in bone loss and increased risk of fracture. After menopause, the risk of fractures increases due to the coupled nature of bone remodeling, leading to bone loss and increased risk of fracture.

Ibandronate sodium is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents. Ibandronate sodium has the following structural formula:

\[
\text{C}_9\text{H}_{22}\text{NO}_7\text{P}_2\text{Na}_2
\]

CLINICAL PHARMACOLOGY: The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which underlies its antiresorptive effect. Ibandronate is a pyrophosphate with the chemical name for ibandronate sodium is 3-(N2-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt.

Mechanism of Action: The bone reabsorption and resorption phase are coupled processes. During bone resorption, osteoclasts release matrix metalloproteinases that degrade the organic and inorganic components of bone matrix, resulting in bone loss and increased risk of fracture. After menopause, the risk of fractures increases due to the coupled nature of bone remodeling, leading to bone loss and increased risk of fracture.

Ibandronate sodium is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents. Ibandronate sodium has the following structural formula:

\[
\text{C}_9\text{H}_{22}\text{NO}_7\text{P}_2\text{Na}_2
\]

CLINICAL PHARMACOLOGY: The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which underlies its antiresorptive effect. Ibandronate is a pyrophosphate with the chemical name for ibandronate sodium is 3-(N2-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt.

Mechanism of Action: The bone reabsorption and resorption phase are coupled processes. During bone resorption, osteoclasts release matrix metalloproteinases that degrade the organic and inorganic components of bone matrix, resulting in bone loss and increased risk of fracture. After menopause, the risk of fractures increases due to the coupled nature of bone remodeling, leading to bone loss and increased risk of fracture.

Ibandronate sodium is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents. Ibandronate sodium has the following structural formula:

\[
\text{C}_9\text{H}_{22}\text{NO}_7\text{P}_2\text{Na}_2
\]

CLINICAL PHARMACOLOGY: The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which underlies its antiresorptive effect. Ibandronate is a pyrophosphate with the chemical name for ibandronate sodium is 3-(N2-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt.

Mechanism of Action: The bone reabsorption and resorption phase are coupled processes. During bone resorption, osteoclasts release matrix metalloproteinases that degrade the organic and inorganic components of bone matrix, resulting in bone loss and increased risk of fracture. After menopause, the risk of fractures increases due to the coupled nature of bone remodeling, leading to bone loss and increased risk of fracture.

Ibandronate sodium is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents. Ibandronate sodium has the following structural formula:

\[
\text{C}_9\text{H}_{22}\text{NO}_7\text{P}_2\text{Na}_2
\]

CLINICAL PHARMACOLOGY: The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which underlies its antiresorptive effect. Ibandronate is a pyrophosphate with the chemical name for ibandronate sodium is 3-(N2-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt.
BONIVA (ibandronate sodium)
ELECTRONIC APPLICATION

BONIVA injection should not be administered in more than 3 ml at any time. IV push should be administered at a rate of 3 mg over 3 minutes. Do not administer BONIVA injection more frequently than once every 3 months. Patients must not receive other bisphosphonates or denosumab during treatment with BONIVA.

Drug Interactions
See CLINICAL PHARMACOLOGY: Drug Interactions.

Drug/Laboratory Test Interactions
Bisphosphonates may interfere with the use of bone-imaging agents. Specific studies with bisphosphonates have not been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies of intravenous BONIVA were conducted in rats and rabbits. In 21-week carcinogenicity study doses of 3.5 or 45 mg/kg/day were administered by intravenous injection to rats. At 45 mg/kg/day, there were no significant differences observed in tumor incidence, multiplicity, or site compared to controls. At 3.5 mg/kg/day, treatment-related increases in lung, kidney, liver, and stomach tumors were noted.

In pregnant rabbits given intravenous doses of 0.03, 0.07 or 0.2 mg/kg/day during organogenesis, ibandronate was present in maternal plasma and fetal milk. In pregnant rats given intravenous doses of 0.08 mg/kg/day, ibandronate was present in rat milk. In lactating rats treated with intravenous doses of 0.08 mg/kg/day, ibandronate was present in rat milk. There was an increased incidence of hypocalcemia and dystocia. The risk/benefit relationship of the use of BONIVA injection in pregnant women should be considered by the prescriber. In pregnant rabbits given intravenous doses of 0.03, 0.07 or 0.2 mg/kg/day during organogenesis, the plasma and milk concentration of ibandronate was similar to that expected in the human plasma and milk concentration at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison.

There was no evidence for a reductive or clastogenic potential of ibandronate in the Salmonella/microsome test. No mutagenic activity of ibandronate was observed in the mouse bone marrow cell mutation test (Ames test). Ibandronate was negative in the mouse lymphoma assay (C3H10T1/2). Ibandronate was not mutagenic in five different bacterial tester strains and three mammalian cells in vitro. In the mouse micronucleus test for chromosomal damage, ibandronate was not mutagenic.

In vivo studies with ibandronate have not been performed.

Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal mortality (24% at the 3 mg/kg/day dose and 40% at the 10 mg/kg/day dose). There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following tests: the in vivo mouse micronucleus test; the in vitro assays for gene mutation, chromosomal aberrations, inducible DNA synthesis, and chromosomal breakage in vitro; and the mouse and rat spermatogonial transplantation test.

Bisphosphonates have been shown to be carcinogenic in rats and mice. The mode of action and the mechanism by which bisphosphonates cause neoplasia is not known. Cancers that often develop in rats include hematopoietic, lymphoreticular, connective tissue, and adrenal cancers, and adenocarcinomas of the liver, stomach, pancreas, and lung. These cancers are based on the increased number of rats observed in treatments compared to controls. There was no evidence of increased lymphoreticular neoplasia in rats treated with ibandronate. There was no evidence of increased lymphoreticular neoplasia in rats treated with ibandronate. There was no evidence of increased lymphoreticular neoplasia in rats treated with ibandronate.

There was no evidence of a carcinogenic potential of ibandronate in the following tests: the in vivo mouse micronucleus test; the in vitro assays for gene mutation, chromosomal aberrations, inducible DNA synthesis, and chromosomal breakage in vitro; and the mouse and rat spermatogonial transplantation test.

There was no evidence of a carcinogenic potential of ibandronate in the following tests: the in vivo mouse micronucleus test; the in vitro assays for gene mutation, chromosomal aberrations, inducible DNA synthesis, and chromosomal breakage in vitro; and the mouse and rat spermatogonial transplantation test.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into bone is variable with oral ibandronate. As expected with bisphosphonate treatment, a decrease in serum calcium levels may occur, especially with the rapid loss of extracellular calcium from the skeleton and the increase in bone turnover. Serum calcium concentrations should be assessed in patients treated with BONIVA injection. In clinical studies, serum calcium concentrations were within normal limits. Long-term administration of ibandronate may increase the risk of renal function impairment, especially in patients with impaired renal function. Ibandronate is not expected to affect serum creatinine concentrations.

A summary of adverse events reported during the clinical evaluation of BONIVA is provided in Table 4. Table 4 gives the percentage of patients who withdrew from treatment due to adverse events, the percentage of patients who withdrew from treatment due to local reactions at the injection site, and the percentage of patients who withdrew from treatment due to deterioration of hepatic or renal function. The overall incidence of patients with APR-like events was 4% in the BONIVA 3 mg daily oral tablet group. The percentage of patients who withdrew from treatment due to local reactions at the injection site was 3% in the BONIVA 3 mg daily oral tablet group. The percentage of patients who withdrew from treatment due to deterioration of hepatic or renal function was 0.3% in the BONIVA 3 mg daily oral tablet group.

Table 4 Adverse Events With an Incidence of at Least 2% in Patients Treated With BONIVA

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>BONIVA (3 mg) (n=364)</th>
<th>Placebo (n=373)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>4.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.4%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Local reactions at injection site</td>
<td>1.7%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

In the BONIVA 3 mg daily oral tablet group, the percentage of patients who withdrew from treatment due to local reactions at the injection site was 3% in the BONIVA 3 mg daily oral tablet group. The percentage of patients who withdrew from treatment due to deterioration of hepatic or renal function was 0.3% in the BONIVA 3 mg daily oral tablet group.

Table 4: Adverse Events With an Incidence of at Least 2% in Patients Treated With BONIVA

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>BONIVA (3 mg) (n=364)</th>
<th>Placebo (n=373)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>4.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.4%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Local reactions at injection site</td>
<td>1.7%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

In the BONIVA 3 mg daily oral tablet group, the percentage of patients who withdrew from treatment due to local reactions at the injection site was 3% in the BONIVA 3 mg daily oral tablet group. The percentage of patients who withdrew from treatment due to deterioration of hepatic or renal function was 0.3% in the BONIVA 3 mg daily oral tablet group.

Oxycodone and nalbuphine were administered to patients who required analgesia due to acute pain associated with rib fracture or osteoporotic fracture. The majority of patients who required analgesia were patients who had undergone surgery for osteoporotic vertebral fracture. The majority of patients who received oxycodone and nalbuphine were patients who had undergone surgery for osteoporotic vertebral fracture. The majority of patients who received oxycodone and nalbuphine were patients who had undergone surgery for osteoporotic vertebral fracture. The majority of patients who received oxycodone and nalbuphine were patients who had undergone surgery for osteoporotic vertebral fracture. The majority of patients who received oxycodone and nalbuphine were patients who had undergone surgery for osteoporotic vertebral fracture.
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.

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

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 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 1-888-MY-BONIVA® or visit www.myboniva.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

BONIVA® is a registered trademark of Roche Therapeutics Inc.

Distributed by:

**Roche Pharmaceuticals**

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1189

Co-promoted by Roche Laboratories Inc. and

**GlaxoSmithKline**

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised: January 2006