

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**NDA 21455/S-007**

*Trade Name:* **BONIVA**

*Generic Name:* **Ibandronate Sodium**

*Sponsor:* **Hoffman-La Roche, Inc.**

*Approval Date:* 11/28/2008

*Indications:* BONIVA is indicated for the treatment and prevention of osteoporosis in postmenopausal women. BONIVA increases bone mineral density (BMD) and reduces the incidence of vertebral fractures.

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*APPLICATION NUMBER:*  
**NDA 21455/S-007**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-455/S-007

Hoffman-La Roche, Inc.  
Attention: Ruben Diaz  
Associate Director, Regulatory Affairs  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Mr. Diaz:

Please refer to your supplemental new drug application dated January 25, 2008, received January 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Boniva (ibandronate sodium) tablets.

We acknowledge receipt of your submissions dated March 27, 2008, April 23, 2008, May 22, 2008, August 11, 2008, October 27, 2008, November 21, 2008, and November 24, 2008.

This supplemental new drug application provides for the additional indication for use of Boniva (ibandronate sodium) tablets, 150 mg, for the prevention of osteoporosis in postmenopausal women.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-455/S-007."

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for the prevention of osteoporosis in postmenopausal women because studies are impossible given the lack of pediatric patients with postmenopausal osteoporosis.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

NDA 21-455/S-007

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If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

*{See appended electronic signature page}*

Scott Monroe, M.D.  
Director  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Scott Monroe  
11/28/2008 10:38:27 AM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 21455/S-007**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BONIVA Tablets safely and effectively. See full prescribing information for BONIVA Tablets.

### BONIVA® (ibandronate sodium) Tablets

Initial U.S. Approval: 2003

#### INDICATIONS AND USAGE

BONIVA is a bisphosphonate indicated for the treatment and prevention of postmenopausal osteoporosis. (1.1)

#### DOSAGE AND ADMINISTRATION

One 150 mg tablet taken once monthly or one 2.5 mg tablet taken once daily (2.1)

Dosing instructions (2.2)

- Swallow whole tablet with 6-8 oz of plain water only, at least 60 minutes before the first food, beverage, or medication of the day.
- Do not lie down for at least 60 minutes after taking BONIVA.
- Do not eat, drink (except for water), or take other medication for 60 minutes after taking BONIVA.

#### DOSAGE FORMS AND STRENGTHS

Tablets: 2.5 mg, 150 mg (3)

#### CONTRAINDICATIONS

- Hypersensitivity to BONIVA (4)
- Hypocalcemia (4)
- Inability to stand or sit upright for at least 60 minutes (4)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Treatment and Prevention of Postmenopausal Osteoporosis

### 2 DOSAGE AND ADMINISTRATION

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- 2.2 Dosing Instructions
- 2.3 Recommendations for Calcium and Vitamin D Supplementation
- 2.4 Use in Specific Populations

### 3 DOSAGE FORMS AND STRENGTHS

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### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy: Category C
- 8.3 Nursing Mothers

## WARNINGS AND PRECAUTIONS

- Upper gastrointestinal (GI) irritation may occur. Follow dosing instructions to minimize GI disorders. Discontinue use if new or worsening symptoms occur. (5.1)
- Hypocalcemia may worsen during treatment. Correct hypocalcemia before use. (5.2)
- Severe bone, joint, and muscle pain may occur. Consider discontinuing use if symptoms develop. (5.3)
- Osteonecrosis of the jaw has been reported. (5.4)

## ADVERSE REACTIONS

The most common adverse reactions (>5%) are back pain, dyspepsia, pain in extremity, diarrhea, headache, and myalgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Roche at 1-800-526-6367 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

- Calcium supplements, antacids and some oral medications may interfere with absorption of ibandronate. (7.1)
- Use caution when co-prescribing aspirin/nonsteroidal anti-inflammatory drugs that may worsen gastrointestinal irritation. (7.2)

## USE IN SPECIFIC POPULATIONS

BONIVA is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min). (5.5, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2008

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Treatment and Prevention of Postmenopausal Osteoporosis

BONIVA is indicated for the treatment and prevention of osteoporosis in postmenopausal women. BONIVA increases bone mineral density (BMD) and reduces the incidence of vertebral fractures.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1. Dose

The dose of BONIVA is either one 150 mg tablet taken once monthly on the same date each month or one 2.5 mg tablet taken once daily.

#### 2.2 Dosing Instructions

- To maximize absorption and clinical benefit, BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day or before taking any oral medication or supplementation, including calcium, antacids, or vitamins (*see DRUG INTERACTIONS [7.1]*).
- To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA (*see WARNINGS AND PRECAUTIONS [5.1]*).
- Patients should not eat, drink anything except water, or take other medications for at least 60 minutes after taking BONIVA.
- Plain water is the only drink that should be taken with BONIVA. Note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.
- The BONIVA 150 mg tablet should be taken on the same date each month (i.e., the patient's BONIVA day).
- The patient must not take two 150 mg tablets within the same week.
- If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is more than 7 days away, the patient should be instructed to take one BONIVA 150 mg tablet in the morning following the date that it is remembered. The patient should then return to taking one BONIVA 150 mg tablet every month in the morning of their chosen day, according to their original schedule.
- If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until the subsequent month's scheduled BONIVA day to take their tablet. The patient should then return to taking one BONIVA 150 mg tablet every month in the morning of their chosen day, according to their original schedule.

#### 2.3 Recommendations for Calcium and Vitamin D Supplementation

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (*see DRUG INTERACTIONS [7.1]*).

#### 2.4 Use in Specific Populations

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

No dose adjustment is necessary for patients with mild or moderate renal impairment.

No dose adjustment is necessary for the elderly, or for patients with hepatic impairment.

### **3 DOSAGE FORMS AND STRENGTHS**

Tablets, 2.5 mg and 150 mg

### **4 CONTRAINDICATIONS**

- Known hypersensitivity to BONIVA or to any of its excipients (*see ADVERSE REACTIONS [6.2]*).
- Hypocalcemia (*see WARNINGS AND PRECAUTIONS [5.2]*)
- Inability to stand or sit upright for at least 60 minutes (*see DOSAGE AND ADMINISTRATION [2.2]*, *WARNINGS AND PRECAUTIONS [5.1]*)

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Upper Gastrointestinal Adverse Reactions**

BONIVA, like other bisphosphonates administered orally, may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer. Advise patients to comply with the dosing instructions to minimize the risk of these effects. Discontinue use if new or worsening symptoms develop (*see DOSAGE AND ADMINISTRATION [2.2]*, *ADVERSE REACTIONS [6]*).

#### **5.2 Hypocalcemia and Mineral Metabolism**

Treat hypocalcemia and other disturbances of bone and mineral metabolism before starting BONIVA therapy. Adequate intake of calcium and vitamin D is important in all patients to prevent hypocalcemia (*see DOSAGE AND ADMINISTRATION [2.3]*). Hypocalcemia following dosing has been reported postmarketing.

#### **5.3 Musculoskeletal Pain**

Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking BONIVA and other bisphosphonates (*see ADVERSE REACTIONS [6]*). The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.

#### **5.4 Jaw Osteonecrosis**

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (e.g., anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally (*see ADVERSE REACTIONS [6.2]*).

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

#### **5.5 Severe Renal Impairment**

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

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### Treatment and Prevention of Postmenopausal Osteoporosis

##### Daily Dosing

The safety of BONIVA 2.5 mg once daily in the treatment and prevention of postmenopausal osteoporosis was assessed in 3577 patients aged 41 – 82 years. The duration of the trials was 2 to 3 years, with 1134 patients exposed to placebo and 1140 exposed to BONIVA 2.5 mg. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors and H2 antagonists were included in these clinical trials. All patients received 500 mg calcium plus 400 IU vitamin D supplementation daily.

The incidence of all-cause mortality was 1% in the placebo group and 1.2% in the BONIVA 2.5 mg daily group. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIVA 2.5 mg daily group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily group and the placebo group. *Table 1* lists adverse events from the treatment and prevention studies reported in  $\geq 2\%$  of patients and more frequently in patients treated daily with BONIVA than patients treated with placebo.

**Table 1 Adverse Events Occurring at a Frequency  $\geq 2\%$  and More Frequently in Patients Treated with BONIVA than in Patients Treated with Placebo Daily in the Osteoporosis Treatment and Prevention Studies**

<b>Body System</b>	<b>Placebo % (n=1134)</b>	<b>BONIVA 2.5 mg % (n=1140)</b>
<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

#### *Gastrointestinal Adverse Events*

The incidence of adverse events in the placebo and BONIVA 2.5 mg daily groups were: dyspepsia (10% vs. 12%), diarrhea (5% vs. 7%), and abdominal pain (5% vs. 6%).

#### *Musculoskeletal Adverse Events*

The incidence of adverse events in the placebo and BONIVA 2.5 mg daily groups were: back pain (12% vs. 14%), arthralgia (14% vs. 14%) and myalgia (5% vs. 6%).

#### *Ocular Adverse Events*

Reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as iritis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued. There were no reports of ocular inflammation in studies with BONIVA 2.5 mg daily.

### Monthly Dosing

The safety of BONIVA 150 mg once monthly in the treatment of postmenopausal osteoporosis was assessed in a two year trial which enrolled 1583 patients aged 54 – 81 years, with 395 patients exposed to BONIVA 2.5 mg daily and 396 exposed to BONIVA 150 mg monthly. Patients with active or significant pre-existing gastrointestinal disease were excluded from this trial. Patients with dyspepsia or concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors and H2 antagonists were included in this study. All patients received 500 mg calcium plus 400 IU vitamin D supplementation daily.

After one year, the incidence of all-cause mortality was 0.3% in both the BONIVA 2.5 mg daily group and the BONIVA 150 mg monthly group. The incidence of serious adverse events was 5% in the BONIVA 2.5 mg daily group and 7% in the BONIVA 150 mg monthly group. The percentage of patients who withdrew from treatment due to adverse events was 9% in the BONIVA 2.5 mg daily group and 8% in the BONIVA 150 mg monthly group. *Table 2* lists the adverse events reported in  $\geq 2\%$  of patients.

**Table 2 Adverse Events with an Incidence of at Least 2% in Patients Treated with BONIVA 2.5 mg Daily or 150 mg Once-Monthly for Treatment of Postmenopausal Osteoporosis**

<b>Body System/Adverse Event</b>	<b>BONIVA 2.5 mg Daily % (n=395)</b>	<b>BONIVA 150 mg Monthly % (n=396)</b>
<b>Vascular Disorders</b>		
Hypertension	7.3	6.3
<b>Gastrointestinal Disorders</b>		
Dyspepsia	7.1	5.6
Nausea	4.8	5.1
Diarrhea	4.1	5.1
Constipation	2.5	4.0
Abdominal Pain <sup>a</sup>	5.3	7.8
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	3.5	5.6
Back Pain	4.3	4.5
Pain in Extremity	1.3	4.0
Localized Osteoarthritis	1.3	3.0
Myalgia	0.8	2.0
Muscle Cramp	2.0	1.8
<b>Infections and Infestations</b>		
Influenza	3.8	4.0
Nasopharyngitis	4.3	3.5
Bronchitis	3.5	2.5
Urinary Tract Infection	1.8	2.3
Upper Respiratory Tract Infection	2.0	2.0
<b>Nervous System Disorders</b>		
Headache	4.1	3.3
Dizziness	1.0	2.3
<b>General Disorders and Administration Site Conditions</b>		
Influenza-like Illness <sup>b</sup>	0.8	3.3
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash <sup>c</sup>	1.3	2.3
<b>Psychiatric Disorders</b>		
Insomnia	0.8	2.0

<sup>a</sup> Combination of abdominal pain and abdominal pain upper

<sup>b</sup> Combination of influenza-like illness and acute phase reaction

<sup>c</sup> Combination of rash pruritic, rash macular, rash papular, rash generalized, rash erythematous, dermatitis, dermatitis allergic, dermatitis medicamentosa, erythema and exanthem

#### *Gastrointestinal Adverse Events*

The incidence of adverse events in the BONIVA 2.5 mg daily and BONIVA 150 mg monthly groups were: dyspepsia (7% vs. 6%), diarrhea (4% vs. 5%), and abdominal pain (5% vs. 8%).

#### *Musculoskeletal Adverse Events*

The incidence of adverse events in the BONIVA 2.5 mg daily and BONIVA 150 mg monthly groups were: back pain (4% vs. 5%), arthralgia (4% vs. 6%) and myalgia (1% vs. 2%).

### *Acute Phase Reactions*

Symptoms consistent with acute phase reactions have been reported with bisphosphonate use. Over the two years of the study, the overall incidence of acute phase reaction symptoms was 3% in the BONIVA 2.5 mg daily group and 9% in the BONIVA 150 mg monthly group. These incidence rates are based on the reporting of any of 33 acute-phase reaction like symptoms within 3 days of the monthly dosing and lasting 7 days or less. Influenza like illness was reported in no patients in the BONIVA 2.5 mg daily group and 2% in the BONIVA 150 mg monthly group.

### *Ocular Adverse Events*

Two patients who received BONIVA 150 mg once-monthly experienced ocular inflammation, one was a case of uveitis and the other scleritis.

One hundred sixty (160) postmenopausal women without osteoporosis participated in a 1-year, double-blind, placebo-controlled study of BONIVA 150 mg once-monthly for prevention of bone loss. Seventy-seven subjects received BONIVA and 83 subjects received placebo. The overall pattern of adverse events was similar to that previously observed.

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of BONIVA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### Hypersensitivity

Allergic reactions including anaphylaxis, angioedema, bronchospasm and rash have been reported (*see CONTRAINDICATIONS [4]*).

### Hypocalcemia

Hypocalcemia has been reported in patients treated with BONIVA (*see WARNINGS AND PRECAUTIONS [5.2]*).

### Musculoskeletal Pain

Bone, joint, or muscle pain (musculoskeletal pain), described as severe or incapacitating, has been reported (*see WARNINGS AND PRECAUTIONS [5.3]*).

### Jaw Osteonecrosis

Osteonecrosis of the jaw has been reported in patients treated with BONIVA (*see WARNINGS AND PRECAUTIONS [5.4]*).

## **7 DRUG INTERACTIONS**

### **7.1 Calcium Supplements/Antacids**

Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of BONIVA. BONIVA should be taken at least 60 minutes before any oral medications, including medications containing multivalent cations (such as antacids, supplements or vitamins). Also, patients should wait at least 60 minutes after dosing before taking any other oral medications (*see PATIENT COUNSELING INFORMATION [17.1]*).

### **7.2 Aspirin/Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

Because aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with BONIVA.

### 7.3 H2 Blockers

In healthy volunteers, co-administration with ranitidine resulted in a 20% increased bioavailability of ibandronate, which was not considered to be clinically relevant (*see CLINICAL PHARMACOLOGY [12.3]*).

### 7.4 Drug/Laboratory Test Interactions

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy: Category C

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

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

In female rats given ibandronate orally at doses  $\geq 3$  times human exposure at the recommended daily oral dose of 2.5 mg or  $\geq 1$  times human exposure at the recommended once-monthly oral dose of 150 mg beginning 14 days before mating and continuing through lactation, maternal deaths were observed at the time of delivery in all dose groups. Perinatal pup loss in dams given 45 times human exposure at the recommended daily dose and 13 times the recommended once-monthly dose was likely related to maternal dystocia. Calcium supplementation did not completely prevent dystocia and periparturient mortality in any of the treated groups at  $\geq 16$  times the recommended daily dose and  $\geq 4.6$  times the recommended once-monthly dose. A low incidence of postimplantation loss was observed in rats treated from 14 days before mating throughout lactation or during gestation, only at doses causing maternal dystocia and periparturient mortality. In pregnant rats dosed orally from gestation day 17 through lactation day 21 (following closure of the hard palate through weaning), maternal toxicity, including dystocia and mortality, fetal perinatal and postnatal mortality, were observed at doses equivalent to human exposure at the recommended daily and  $\geq 4$  times the recommended once-monthly dose. Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia (*see NONCLINICAL TOXICOLOGY [13.2]*).

Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at oral doses 30 times the human exposure at the recommended daily oral dose of 2.5 mg and  $\geq 9$  times the recommended once-monthly oral dose of 150 mg. Impaired pup neuromuscular development (cliff avoidance test) was observed at 45 times human exposure at the daily dose and 13 times the once-monthly dose (*see NONCLINICAL TOXICOLOGY [13.2]*).

In pregnant rabbits treated orally with ibandronate during gestation at doses  $\geq 8$  times the recommended human daily oral dose of 2.5 mg and  $\geq 4$  times the recommended human once-monthly oral dose of 150 mg, dose-related maternal mortality was observed in all treatment groups. The deaths occurred prior to parturition and were associated with lung edema and hemorrhage. No significant fetal anomalies were observed (*see NONCLINICAL TOXICOLOGY [13.2]*).

### 8.3 Nursing Mothers

It is not known whether BONIVA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BONIVA is administered to a nursing woman. In lactating rats treated with intravenous doses, ibandronate was present in breast milk from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations.

### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### 8.5 Geriatric Use

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

### 8.6 Renal Impairment

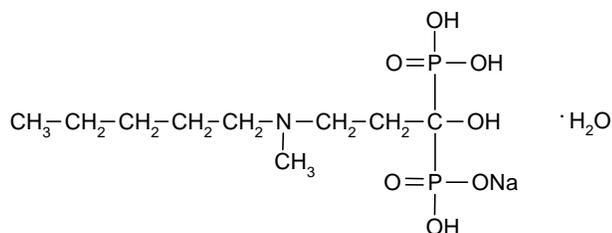
BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min).

## 10 OVERDOSAGE

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

## 11 DESCRIPTION

BONIVA (ibandronate sodium) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. The chemical name for ibandronate sodium is 3-(*N*-methyl-*N*-pentyl) amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate with the molecular formula  $C_9H_{22}NO_7P_2Na \cdot H_2O$  and a molecular weight of 359.24. 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:



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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 Pharmacodynamics

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

BONIVA produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases of biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked C-telopeptide of Type I collagen) in the daily dose range of 0.25 mg to 5 mg and once-monthly doses from 100 mg to 150 mg in postmenopausal women.

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

In a 1-year, study comparing once-monthly vs. once-daily oral dosing regimens, the median decrease from baseline in serum CTX values was -76% for patients treated with the 150 mg once-monthly regimen and -67% for patients treated with the 2.5 mg daily regimen. In a 1-year, prevention study comparing BONIVA 150 mg once-monthly to placebo, the median placebo-subtracted decrease in sCTX was -49.8%.

### 12.3 Pharmacokinetics

#### Absorption

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

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

## **Distribution**

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

## **Metabolism**

Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system. Ibandronate is eliminated by renal excretion. Based on a rat study, the ibandronate secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other drugs. There is no evidence that ibandronate is metabolized in humans.

## **Elimination**

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

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

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

## **Specific Populations**

### Pediatrics

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

### Geriatric

Because ibandronate is not known to be metabolized, the only difference in ibandronate elimination for geriatric patients versus younger patients is expected to relate to progressive age-related changes in renal function.

### Gender

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

### Race

Pharmacokinetic differences due to race have not been studied.

### Renal Impairment

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

Following a single dose of 0.5 mg ibandronate by intravenous administration, patients with CLcr 40 to 70 mL/min had 55% higher exposure ( $AUC_{\infty}$ ) than the exposure observed in subjects with CLcr >90 mL/min. Patients with CLcr <30 mL/min had more than a two-fold increase in exposure compared to the exposure for healthy subjects (*see DOSAGE AND ADMINISTRATION [2.4]*).

### Hepatic Impairment

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

### **Drug Interactions**

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

### H2 Blockers

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

## **13 NONCLINICAL TOXICOLOGY**

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

#### **Carcinogenesis**

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

#### **Mutagenesis**

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

## **Impairment of Fertility**

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

## **13.2 Animal Reproductive and Developmental Toxicology**

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

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

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

## **13.3 Animal Pharmacology**

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

Long-term daily or once-monthly intermittent administration of ibandronate to ovariectomized rats or monkeys was associated with suppression of bone turnover and increases in bone mass. In both rats and monkeys, vertebral BMD, trabecular density, and biomechanical strength were increased dose-dependently at doses up to 15 times the recommended human daily oral dose of 2.5 mg, or cumulative monthly doses up to 8 times (rat) or 6 times (monkey) the recommended human once-monthly oral dose of 150 mg, based on body surface area ( $\text{mg}/\text{m}^2$ ) or AUC comparison. In monkeys, ibandronate maintained the positive correlation between bone mass and strength at the ulna and femoral neck. New bone formed in the presence of ibandronate had normal histologic structure and did not show mineralization defects.

## **14 CLINICAL STUDIES**

### **14.1 Treatment of Postmenopausal Osteoporosis**

#### **Daily Dosing**

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

#### Effect on Fracture Incidence

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

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

	Proportion of Patients with Fracture (%)			
	Placebo n=975	BONIVA 2.5 mg Daily n=977	Absolute Risk Reduction (%) 95% CI	Relative Risk Reduction (%) 95% CI
New Vertebral Fracture 0-3 Year	9.6	4.7	4.9 (2.3, 7.4)	52 <sup>**</sup> (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)

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

\*\*p=0.0003 vs. placebo

BONIVA 2.5 mg daily did not reduce the incidence of nonvertebral fractures (secondary efficacy measure). There was a similar number of nonvertebral osteoporotic fractures at 3 years reported in women treated with BONIVA 2.5 mg daily [9.1%, (95% CI: 7.1%, 11.1%)] and placebo [8.2%, (95% CI: 6.3%, 10.2%)]. The two treatment groups were also similar with regard to the number of fractures reported at the individual nonvertebral sites: pelvis, femur, wrist, forearm, rib, and hip.

#### Bone Mineral Density (BMD)

BONIVA significantly increased BMD at the lumbar spine and hip relative to treatment with placebo. In the 3-year osteoporosis treatment study, BONIVA 2.5 mg daily produced increases in lumbar spine BMD that were progressive over 3 years of treatment and were statistically significant relative to placebo at 6 months and at all later time points. Lumbar spine BMD increased by 6.4% after 3 years of treatment with 2.5 mg daily BONIVA compared with 1.4% in the placebo group. *Table 4* displays the significant increases in BMD seen at the lumbar spine, total hip, femoral neck, and trochanter compared to placebo. Thus, overall BONIVA reverses the loss of BMD, a central factor in the progression of osteoporosis.

**Table 4 Mean Percent Change in BMD from Baseline to Endpoint in Patients Treated Daily with BONIVA 2.5 mg or Placebo in the 3-Year Osteoporosis Treatment Study\***

	<b>Placebo</b>	<b>BONIVA 2.5 mg Daily</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)

\*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 postbaseline value prior to the study's last time point is used.

### Bone Histology

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

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

### **Once-Monthly Dosing**

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

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

## **14.2 Prevention of Postmenopausal Osteoporosis**

### **Daily Dosing**

The safety and effectiveness of BONIVA 2.5 mg daily for the prevention of postmenopausal osteoporosis were demonstrated in a randomized, double-blind, placebo-controlled 2-year study (Prevention Study) of 653 postmenopausal women without osteoporosis at baseline. Women were aged 41 to 82 years, were on average 8.5 years postmenopause, and had lumbar spine BMD T-scores >-2.5. Women were stratified according

to time since menopause (1 to 3 years, >3 years) and baseline lumbar spine BMD (T-score: >-1, -1 to -2.5). The study compared daily BONIVA at three dose levels (0.5 mg, 1.0 mg, 2.5 mg) with placebo. All women received 500 mg of supplemental calcium per day.

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

Compared with placebo, treatment with BONIVA 2.5 mg daily increased BMD of the total hip by 1.8%, the femoral neck by 2.0%, and the trochanter by 2.1%.

### **Once-Monthly Dosing**

BONIVA 150 mg once-monthly prevented bone loss in a majority (88.2%) of women in a randomized, double-blind, placebo-controlled 1-year study (Monthly Prevention Study) of 160 postmenopausal women with low bone mass at baseline (T-score of -1 to -2.5). Women, aged 46 to 60 years, were on average 5.4 years postmenopause. All women received 400 IU of vitamin D and 500 mg calcium supplementation daily.

The primary efficacy measure was the relative change in BMD at the lumbar spine after 1 year of treatment. BONIVA 150 mg once-monthly resulted in a mean increase in lumbar spine BMD of 4.12% (95% confidence interval 2.96 – 5.28) compared with placebo following 1 year of treatment ( $p < 0.0001$ ), based on a 3.73% and -0.39% mean change in BMD from baseline in the 150 mg once-monthly BONIVA and placebo treatment groups, respectively. BMD at other skeletal sites was also increased relative to baseline values.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**

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

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

### **16.2 Storage and Handling**

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

## **17 PATIENT COUNSELING INFORMATION**

See *FDA-APPROVED PATIENT LABELING* (17.2)

### **17.1 Information for Patients**

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

- BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day and before taking any oral medication or supplementation including calcium, antacids or vitamins (*see DRUG INTERACTIONS* [7.1]).

- To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA.
- Patients should not eat, drink anything except for water, or take other medications for 60 minutes after taking BONIVA.
- Plain water is the only drink that should be taken with BONIVA. Note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.
- The BONIVA 2.5 mg tablet should be taken at the same time each day.
- If a once-daily dose is missed, the patient should be instructed to skip that dose and return to their normal schedule the next day.
- The patient must not take two 2.5 mg tablets within the same day.
- The BONIVA 150 mg tablet should be taken on the same date each month (i.e., the patient's BONIVA day).
- The patient must not take two 150 mg tablets within the same week.
- If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is more than 7 days away, the patient should be instructed to take one BONIVA 150 mg tablet in the morning following the date that it is remembered (*see DOSAGE AND ADMINISTRATION [2.3]*). The patient should then return to taking one BONIVA 150 mg tablet every month in the morning of their chosen day, according to their original schedule.
- If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until the subsequent month's scheduled BONIVA day to take their tablet. The patient should then return to taking one BONIVA 150 mg tablet every month in the morning of their chosen day, according to their original schedule.

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

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

## 17.2 FDA-Approved Patient Labeling

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

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

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

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

## What is BONIVA?

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

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

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

## Who should not take BONIVA?

Do not take BONIVA if you:

- have low blood calcium (hypocalcemia)
- cannot sit or stand up for at least 60 minutes
- have kidneys that work very poorly
- are allergic to ibandronate sodium or any of the other ingredients of BONIVA (see the end of this leaflet for a list of all the ingredients in BONIVA)

## Tell your health care provider before using BONIVA:

- if you are pregnant or planning to become pregnant. It is not known if BONIVA can harm your unborn baby.
- if you are breast-feeding. It is not known if BONIVA passes into your milk and if it can harm your baby.
- have swallowing problems or other problems with your esophagus (the tube that connects your mouth and stomach)
- if you have kidney problems
- if you are planning a dental procedure such as tooth extraction

**Tell your health care provider (including your dentist) about all the medicines you take** including prescription and non-prescription medicines, vitamins and supplements. Some medicines, especially certain vitamins, supplements, and antacids can stop BONIVA from getting to your bones. This can happen if you take other medicines too close to the time that you take BONIVA (see “[How should I take BONIVA?](#)”).

## How should I take BONIVA?

- Take BONIVA exactly as instructed by your health care provider.
- Take BONIVA first thing in the morning at least 60 minutes before you eat, drink anything other than plain water, or take any other oral medicine.
- Take BONIVA with 6 to 8 ounces (about 1 full cup) of plain water. Do not take it with any drink other than plain water. Do not take it with other drinks, such as mineral water, sparkling water, coffee, tea, dairy drinks (such as milk), or juice.
- Swallow BONIVA whole. Do not chew or suck the tablet or keep it in your mouth to melt or dissolve.
- After taking BONIVA you must wait at least 60 minutes before:
  - Lying down. You may sit, stand, or do normal activities like read the newspaper or take a walk.
  - Eating or drinking anything except for plain water.
  - Taking other oral medicines including vitamins, calcium, or antacids. Take your vitamins, calcium, and antacids at a different time of the day from the time when you take BONIVA.
- If you take too much BONIVA, drink a full glass of milk and call your local poison control center or emergency room right away. Do not make yourself vomit. Do not lie down.

- Keep taking BONIVA for as long as your health care provider tells you. BONIVA will not work if you stop taking it.
- Your health care provider may tell you to exercise and take calcium and vitamin supplements to help your osteoporosis.
- Your health care provider may do a test to measure the thickness (density) of your bones or do other tests to check your progress.

### What is my BONIVA schedule?

#### Schedule for taking BONIVA 2.5 mg once-daily:

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

#### What to do if I miss a daily dose:

- If you forget to take your BONIVA 2.5 mg tablet in the morning, **do not** take it later in the day. Just return to your normal schedule and take 1 tablet the next morning. **Do not** take two tablets on the same day.
- **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.**

#### Schedule for taking BONIVA 150 mg once-monthly:

- Take one BONIVA 150 mg tablet once a month.
- Choose one date of the month (your BONIVA day) that you will remember and that best fits your schedule to take your BONIVA 150 mg tablet.
- Take one BONIVA 150 mg tablet in the morning of your chosen day (see “[How should I take BONIVA?](#)”).

#### What to do if I miss a monthly dose:

- If your next scheduled BONIVA day is more than 7 days away, take one BONIVA 150 mg tablet in the morning following the day that you remember (see “[How should I take BONIVA?](#)”). Then return to taking one BONIVA 150 mg tablet every month in the morning of your chosen day, according to your original schedule.
- **Do not** take two 150 mg tablets within the same week. If your next scheduled BONIVA day is only 1 to 7 days away, **wait** until your next scheduled BONIVA day to take your tablet. Then return to taking one BONIVA 150 mg tablet every month in the morning of your chosen day, according to your original schedule.
- **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 should I avoid while taking BONIVA?

- Do not take other medicines, or eat or drink anything but plain water before you take BONIVA and for at least 60 minutes after you take it.
- Do not lie down for at least 60 minutes after you take BONIVA.

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

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

- **pain or trouble with swallowing**
- **chest pain**
- **very bad heartburn or heartburn that does not get better**

BONIVA MAY CAUSE:

- pain or trouble swallowing (dysphagia)
- heartburn (esophagitis)
- ulcers in your stomach or esophagus (the tube that connects your mouth and stomach)

Common side effects with BONIVA are:

- diarrhea
- pain in extremities (arms or legs)
- dyspepsia (upset stomach)

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

Rarely, patients have reported allergic and skin reactions. Contact your health care provider if you develop any symptoms of an allergic reaction including skin rash (with or without blisters), hives, wheezing, or swelling of the face, lips, tongue or throat. Get medical help right away if you have trouble breathing, swallowing or feel light-headed.

Rarely, patients have reported severe bone, joint, and/or muscle pain starting within one day to several months after beginning to take, by mouth, 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.

Rarely, patients taking bisphosphonates have reported serious jaw problems associated with delayed healing and infection, often following dental procedures such as tooth extraction. If you experience jaw problems, contact your health care provider and dentist.

## **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.

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**

Do not use BONIVA for a condition for which it was not prescribed. Do not give BONIVA to other people, even if they have the same symptoms you have. It may harm them.

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

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

This summarizes the most important information about BONIVA. 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 that is written for health professionals.

For more information about BONIVA, call 1-888-MY-BONIVA or visit [www.myboniva.com](http://www.myboniva.com).

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

BONIVA (active ingredient): ibandronate sodium

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

BONIVA is a registered trademark of Roche Therapeutics Inc.

Distributed by:



**Pharmaceuticals**

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

Co-promoted by Roche Laboratories Inc. and



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Revised: November 2008

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Scott Monroe  
11/28/2008 10:38:27 AM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**OFFICER/EMPLOYEE LIST**

NDA 21-455 Boniva

List of officers/employees who participated in the decision to approve this application and consented to be identified on this list.

Scott Monroe, M.D., Director, Division of Reproductive and Urologic Products (DRUP)

Lisa Soule, M.D., Medical Team Leader, DRUP

Lynnda L Reid, Ph.D., Pharmacology Supervisor, DRUP

Karl Stiller, R.Ph., Regulatory Project Manager, DRUP

Sharon Kelly, Ph.D., Chemistry Reviewer, Office of New Drug Quality Assessment

Myong-Jin Kim, Pharm.D., Pharmacologist, Office of Clinical Pharmacology

Anastasia Lolas, Ph.D., Microbiologist, Manufacturing Assessment and Pre-Approval Compliance Branch

Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer, Division of Drug Marketing, Advertising and Communications

George Greeley, Regulatory Health Project Manager, Pediatric and Maternal Health Staff

Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**OFFICE DIRECTOR MEMO**

## Division Director Summary Review for Regulatory Action

<b>Date</b>	November 26, 2008
<b>From</b>	Scott Monroe, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA</b>	NDA 21-455/SE1-007
<b>Applicant Name</b>	Hoffmann-La Roche, Inc.
<b>Date of Submission</b>	January 25, 2008
<b>PDUFA Goal Date</b>	November 28, 2008
<b>Proprietary Name / Established (USAN) Name</b>	BONIVA <sup>®</sup> Ibandronate sodium
<b>Dosage Forms / Strength</b>	Oral tablet (150 mg)
<b>Proposed New Indication</b>	Prevention of osteoporosis in postmenopausal women
<b>Proposed Regimen</b>	One 150 mg tablet once a month
<b>Action</b>	<i>Approve (see Section 13.1)</i>

<b>Material Reviewed/Consulted OND Action Package, including:</b>	<b>Names of Discipline Reviewers</b>
<b>Medical Officer Review</b>	Lesley Furlong, MD (primary reviewer)
<b>Statistical Review</b>	Stella Grosser, PhD/Mahboob Sobhan, PhD
<b>Pharmacology Toxicology Review</b>	Lynnda Reid, PhD
<b>CMC Review/ONDQA</b>	Sharon Kelly, PhD/Hasmukh Patel, PhD
<b>Microbiology Review</b>	Not required
<b>Clinical Pharmacology Review</b>	Sandhya Apparaju, PhD/Myong-Jin Kim, Pharm.D
<b>DDMAC</b>	Janice Maniwang, Pharm.D, MBA
<b>DSI</b>	Not required
<b>CDTL Review/ OSE/DMEPA</b>	Lisa Soule, MD (medical team leader) Not required

OND      Office of New Drugs  
 DDMAC    Division of Drug Marketing, Advertising, and Communication  
 OSE      Office of Surveillance and Epidemiology  
 DMEPA    Division of Medication Errors Prevention and Analysis  
 DSI      Division of Scientific Investigations  
 CDTL     Cross-Discipline Team Leader

## 1. INTRODUCTION

The objective of this efficacy supplement (NDA (b) (4)/SE1-007) is to obtain marketing approval for once-monthly ibandronate sodium tablets 150 mg (hereafter referred to as Boniva) for the prevention of osteoporosis in postmenopausal women. Once-monthly Boniva Tablets 150 mg are currently approved for the treatment of osteoporosis in postmenopausal women.

Neither the primary Medical Reviewer nor the medical Team Leader identified any issues during their respective reviews of this efficacy supplement that would preclude approval of Boniva Tablets 150 mg for the proposed indication. The Applicant did not submit any new [chemistry, manufacturing, and control (CMC)], clinical pharmacology, or nonclinical toxicology data, in part, because Boniva Tablets 150 mg is an approved product. In this Memorandum, I will briefly summarize the efficacy and safety findings from the single adequate and well-controlled clinical trial that was submitted in support of the proposed additional indication. Based on my review of this submission, I concur with the recommendations of the primary Medical Reviewer and the medical Team Leader that once-monthly Boniva Tablets 150 mg be approved for the indication of “prevention of osteoporosis in postmenopausal women.”

## 2. BACKGROUND

### 2.1 Description of the Product

Ibandronate sodium (Boniva) is a bisphosphonate that inhibits osteoclast-mediated bone resorption. Bisphosphonates, through their affinity for hydroxyapatite in the bone matrix, inhibit osteoclast activity and decrease bone resorption and bone turnover. Currently, there are 4 bisphosphonates approved in the U.S. for the treatment and/or prevention of postmenopausal osteoporosis (PMO). They are (1) ibandronate (Boniva<sup>®</sup>), (2) alendronate (Fosamax<sup>®</sup>), (3) zoledronic acid (Reclast<sup>®</sup>), and (4) risedronate (Actonel<sup>®</sup>). Three formulations of Boniva, a daily 2.5 mg tablet, a monthly 150 mg tablet, and a 3 mg solution administered intravenously once every 3 months, are currently approved in the U.S. for the prevention and/or treatment of PMO. According to the medical Team Leader, the 150 mg dose has also been approved for treatment of PMO in more than 80 countries, but is not approved for prevention of PMO in any country at this time.

### 2.2 Regulatory History

Boniva Tablets 2.5 mg/day was approved by the Division of Metabolic and Endocrine Products (DMEP) for the treatment of postmenopausal osteoporosis in May 2003. Approval was based, in part, on the Applicant demonstrating that treatment with Boniva 2.5 mg/day for 3 years reduced by approximately 50% the incidence of new morphometric vertebral fractures compared to treatment with placebo. In March 2005, once-monthly Boniva Tablets 150 mg was approved for the treatment of postmenopausal osteoporosis. Approval was based, in part, on the Applicant’s demonstrating in a single clinical trial (Study BM16549) that treatment with once-monthly Boniva 150 mg was non-inferior to treatment with Boniva 2.5 mg/day, in the percent change in lumbar bone mineral density (BMD) from baseline after 12 months of treatment. Subjects enrolled in Study BM16549 were to have had osteoporosis at baseline (i.e., a lumbar BMD T-score of  $\leq -2.5$  at baseline). Because the population of subjects enrolled in Study BM16549 had more extreme bone loss than subjects generally enrolled in osteoporosis prevention studies

(i.e., a baseline BMD T-score between -1.0 and  $> -2.5$ ), the clinical trial did not fully support an osteoporosis prevention indication. DMEP, however, allowed the following statement in the Dosage and Administration section of labeling for Boniva Tablets 150 mg:

*The recommended dose of BONIVA for the prevention of postmenopausal osteoporosis is one 2.5-mg tablet taken once daily. Alternatively, one 150-mg tablet taken once monthly on the exact same date each month may be considered (see Indications and Usage).*

In January 2008, regulatory review and oversight for products for the prevention and/or treatment of osteoporosis was transferred from DMEP to the Division of Reproductive and Urologic Products (DRUP). Because of the transfer of responsibility, this Application has been reviewed by DRUP. All agreements between DMEP and the Applicant in regard to clinical trial design, primary assessment and endpoints (relative change in lumbar BMD from baseline at Month 12 of treatment), and criteria for a successful clinical trial outcome have been accepted by DRUP.

### **2.3 Content of NDA**

In the present submission, the Applicant has provided data from a single adequate and well-controlled clinical trial conducted in postmenopausal women with osteopenia (i.e., a BMD T-score between -1.0 and  $> -2.5$ ) who were treated with either once-monthly Boniva 150 mg or placebo for 12 months. The objective of this study was to support approval of an indication for the prevention of postmenopausal osteoporosis with the once-monthly Boniva Tablet 150 mg dosing regimen. The Application also included a revised Package Insert in Physician Labeling Rule (PLR) format (presently approved labeling for Boniva is not in PLR format). The Application did not include any new [chemistry, manufacturing, and control (CMC)], clinical pharmacology, or nonclinical toxicology data, in part, because Boniva Tablets 150 mg is an approved product.

### **2.4 Recommendations of Primary Medical Reviewer and Medical Team Leader regarding Approvability**

The primary Medical Reviewer, Dr. Lesley Furlong, stated in her review, signed on November 12, 2008:

*“I recommend approval of the application pending agreement on final labeling.”*

The medical Team Leader, Dr. Lisa Soule, stated in her review, signed on November 25, 2008:

*“I recommend that Boniva in the 150 mg dose and once-monthly dose regimen be approved for the indication “prevention of osteoporosis in postmenopausal women.”*

### **Division Director’s Comment**

- *I concur with the recommendations of Dr. Furlong and Dr. Soule.*

### **3. CMC**

The primary Chemistry Reviewer, Sharon Kelly, PhD, made the following statement and recommendation in her review, signed on October 10, 2008:

*“There are no CMC changes. From a CMC perspective, this Supplement can be Approved.”*

#### **Division Director's Comment**

- *I concur with the assessment/recommendation made by Dr. Kelly. There are no outstanding CMC issues.*

#### **4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

No new nonclinical pharmacology/toxicology data were submitted in the present Application. The primary Toxicology Reviewer, Lynnda Reid, Ph.D., made the following recommendations in her review signed October 15, 2008:

- A. *“Recommendation on approvability: Nonclinical data support approval.”*
- B. *“Recommendation for nonclinical studies: None.”*

Dr. Reid also made several recommendations regarding labeling that were subsequently incorporated into final labeling.

#### **Division Director's Comment**

- *I concur with the assessment of Dr. Reid that the nonclinical data that were reviewed in support of earlier NDAs for Boniva for the treatment of postmenopausal osteoporosis support approval of the current efficacy supplement.*

#### **5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS**

The primary Clinical Pharmacology Reviewer, Sandhya Apparaju, PhD, stated the following in her review, which she signed on July 16, 2008:

*“No new Clinical Pharmacology information has been submitted with this efficacy supplement. The new prevention clinical trial employed the approved 150 mg ibandronate tablet formulation. The pharmacokinetics of ibandronate following the 150 mg tablet as well as the drug interaction and special population dosing issues for ibandronate were found to be adequately addressed during the previous NDA.”*

*“The NDA is acceptable from a Clinical Pharmacology perspective provided an agreement can be reached with the sponsor regarding the labeling language.”*

#### **Division Director's Comment**

- *I concur with the conclusions and recommendation of Dr. Apparaju. Labeling submitted by the Applicant on November 21, 2008 was reviewed by Dr. Apparaju and found to be acceptable.*

#### **6. CLINICAL MICROBIOLOGY**

A separate microbiology review was not conducted as the Applicant did not propose any changes in the approved chemistry, manufacturing, and controls (CMC) from those for the currently approved and marketed 150 mg tablet.

#### **7. CLINICAL/STATISTICAL-EFFICACY**

##### **7.1 Overview of Clinical Trial BA18492**

The Applicant submitted data from a single adequate and well-controlled clinical trial. Study BA18492 was a double-blind, randomized, placebo-controlled, multicenter study,

designed to investigate the efficacy and safety of one year of treatment with once-monthly Boniva Tablets 150 mg for the prevention of osteoporosis in postmenopausal osteopenic women. The study was conducted at 10 centers in the United States. One-hundred and sixty (160) women were randomized; 77 received Boniva once monthly, 83 received matching placebo. All subjects also received 500 mg calcium and 400 IU of vitamin D daily. Subjects were stratified by time since menopause (0.5 to 3.0 years and >3.0 years).

Subjects were to be postmenopausal and ambulatory at the beginning of the trial, between the ages of 45 and 60 years old, with a baseline mean lumbar spine BMD T-score of < -1.0 and > -2.5 (L2-L4), and a baseline proximal femur BMD T-score of > -2.5.

The primary efficacy assessment was the relative change (%) in lumbar BMD from baseline at Month 12 of treatment. The safety analysis included all subjects who received treatment. The primary efficacy analysis included all subjects who provided BMD data at Month 12.

## 7.2 DISPOSITION OF SUBJECTS

A slightly greater proportion of subjects in the Boniva treatment group (12/77; 16%) withdrew prematurely from the study than in the placebo group (10/83; 12%) (see Table 1). The difference was largely due to a greater number of discontinuations due to adverse events in the Boniva-treated subjects (see Section 8.2 for further details).

**Table 1 Reasons for Premature Discontinuation (Safety Cohort)**

	<b>Placebo</b> <b>N (% of safety population)</b>	<b>Boniva</b> <b>N (% of safety population)</b>
Safety Population	83 (100)	77 (100)
Completed study	73 (88)	65 (84)
Did not complete	10 (12)	12 (16)
Reason for premature discontinuation		
Adverse event	3 (3.6)	7 (9.1)
Refused treatment	5 (6.0)	3 (3.9)
Failure to return	1 (1.2)	1 (1.3)
Other	1 (1.2)	1 (1.3)

Source: Review of medical Team Leader, Table 3.

## 7.3 Primary Efficacy Findings

The primary analysis was an ANOVA, including treatment group, time since menopause (as a binary variable, defined as per the randomization strata: 0.5-3.0 years; >3.0 years) and baseline BMD (L2-L4) T-score value as independent variables.

The analysis of the primary efficacy assessment yielded a statistically significant result favoring Boniva in terms of the relative change (%) in lumbar BMD from baseline (see Table 2). The adjusted mean percent changes from baseline in lumbar spine BMD were -0.39% and +3.73% for subjects treated with placebo or Boniva, respectively (p <0.0001).

**Table 2 Mean Percent Change from Baseline for Lumbar Spine BMD at Month 12**

	<b>Placebo (n=83)</b>	<b>Boniva (n=77)</b>
Number (%) subjects with BMD data	70 (86%)	68 (88%)
Raw mean % change (SD) in BMD	-0.43 (3.49)	3.58 (3.48)
Adjusted mean % change (SE) in BMD	-0.39 (0.41)	3.73 (0.42)
<b>Treatment effect</b>	--	<b>4.12</b>
95% CI		2.96, 5.28
<b>P-value</b>		<b>&lt;0.0001</b>

Raw mean: data included BMD measurements in which unevaluable and/or fractured vertebrae were identified. "Adjusted" mean data excluded such measurements.

Source: Modified from Table 2 of FDA statistical review.

#### 7.4 Statistical Assessment of Efficacy

The statistical reviewer, Stella Grosser, Ph.D., analyzed the data and conducted sensitivity analyses to account for the subjects who terminated the trial prematurely. To do this, she assigned all Boniva subjects who withdrew the mean change from baseline in lumbar spine BMD that was observed in the placebo group, and did the converse for the early withdrawals in the placebo group. The treatment effect remained large (+2.9%) in favor of Boniva. Dr. Grosser made the following statement in her review dated November 14, 2008:

*“There is a statistically significant difference, in favor of IBN [ibandronate], in relative change from baseline in the mean BMD of the lumbar spine at 12 months. Sensitivity analysis of the primary endpoint, as well as analysis of the secondary endpoints, further support the efficacy of IBN (ibandronate) 150 mg once monthly in the prevention of bone loss in osteopenic women.”*

#### 7.5 Overall Assessment of Efficacy

Study BA18492 supports, by meeting the protocol pre-specified primary efficacy endpoint, the efficacy of once-monthly Boniva Tablets 150 mg for the prevention of osteoporosis in postmenopausal women. The adjusted mean percentage change from baseline in lumbar BMD at treatment Month 12 was +3.73% for 68 subjects treated with Boniva, compared with -0.39% for 70 subjects treated with placebo. The overall treatment effect (i.e., mean difference between the lumbar BMD in the Boniva vs. placebo treatment groups) of + 4.12% was statistically significant (p-value: < 0.0001).

#### Division Director’s Comments

- *No vertebral fractures occurred in either group; however, the study was not powered to show a difference in the risk of vertebral fractures, did not enroll subjects at high risk for fracture, and was only one year in duration.*
- *The findings from Study BA18492, by themselves, would not be sufficient to support the indication of prevention of postmenopausal osteoporosis. The Applicant, however, demonstrated in prior submissions that (1) treatment with Boniva 2.5 mg/day reduced by approximately 50% the incidence of new morphometric vertebral fractures compared to treatment with placebo and (2) treatment with once-monthly Boniva 150 mg was non-inferior to treatment with Boniva 2.5 mg/day, in terms of the percent change in*

*lumbar BMD. By extrapolation from the findings from these 2 earlier studies and the results from Study BA18492, the Applicant has provided adequate data to support the efficacy of once-monthly Boniva 150 mg for the indication of prevention of osteoporosis in postmenopausal women.*

## 8. SAFETY

The primary Medical Reviewer and medical Team Leader have thoroughly reviewed and discussed the safety findings from Study BA18492, as well as the expected risks associated with the use of a bisphosphonate for the prevention or treatment of postmenopausal osteoporosis. In the following review of safety, only the most important safety findings from Study BA18492 are summarized.

### 8.1 Deaths and Other Serious Adverse Events

No deaths were reported during the conduct of Study BA18492.

In Study BA18492, 3 serious adverse events (SAEs) were reported for Boniva-treated subjects and one SAE was reported for a placebo-treated subject (see Table 3). All of the SAEs were judged to be unrelated to treatment by the study investigators.

**Table 3 Serious Adverse Events in Study BA18492**

Subject No.	Treatment Arm	MedDRA Term (Additional Description)	Discontinued from study	Applicant assessment of causality	Reviewer assessment of causality
1015	Boniva	Pyelonephritis (history of bladder prolapse)	No	Unrelated	Unrelated
1367	Boniva	Upper limb fracture (high impact trauma, following fall from a ladder)	Yes	Unrelated	Unrelated
1376	Placebo	Cellulitis (post-traumatic hand infection)	No	Unrelated	Unrelated
1380	Boniva	Chest pain (non-cardiac, diagnosed as GERD*)	Yes	Unrelated	Unrelated

\* GERD = gastroesophageal reflux disease  
Source: Review of medical Team Leader, Table 5.

### Division Director's Comment

- The total number of serious adverse events for a 52-week clinical trial in postmenopausal women with osteopenia is low. The types of reported serious adverse events in the clinical trial do not raise any new safety concern for Boniva.*

Other adverse events of significance included clinical fractures. These occurred in 2 subjects in each treatment arm. Two placebo-treated subjects had foot fractures. One Boniva-treated subject had a Colles fracture and another had a rib and a radial head fracture. All fractures were associated with trauma, and none were attributed to osteopenia, per se. No new vertebral fractures were reported in either treatment group.

## 8.2 Discontinuations for Adverse Events

Seven (7) subjects (9.1%) in the Boniva arm and 3 subjects (3.6%) in the placebo arm discontinued from the trial due to adverse events. Subjects who discontinued because of an adverse event and the associated adverse event(s) are listed in Table 4.

**Table 4 Adverse Events Leading to Premature Subject Discontinuation in Study BA18492**

Subject #	Treatment Arm	Description
1012	Boniva	Gastroesophageal reflux disease (GERD)
1129	Placebo	Periarthritis
1188	Placebo	Heartburn
1192	Boniva	Severe muscle pain
1249	Boniva	Weight increase
1364	Placebo	GERD
1367	Boniva	Traumatic upper limb fracture
1370	Boniva	Flu-like symptoms (headache, myalgia, arthralgia)
1380	Boniva	Chest pain (GERD)
1503	Boniva	Nausea, upset stomach, cramps, fatigue

Source: Review of medical Team Leader, Table 6.

### Division Director's Comments

- *Adverse events leading to subject discontinuation related to GERD occurred more frequently in Boniva-treated subjects than placebo-treated subjects (2 vs. 1). However, an additional placebo-treated subject experienced "heartburn," which may represent a similar disorder.*
- *Severe muscle pain leading to discontinuation was also more common in Boniva-treated subjects than in placebo-treated subjects (2 vs. 0).*
- *The adverse events possibly related to treatment with study drug and which led to subject discontinuation are known to be associated with bisphosphonate treatment and do not raise any new safety concerns.*
- *Both upper gastrointestinal and musculoskeletal adverse events are expected complications of treatment with bisphosphonates and are listed in the Warnings and Precautions Section of labeling.*

## 8.3 Overall Assessment of Safety

Safety data from Study BA18492 submitted in support of this efficacy supplement do not raise any new concerns regarding the safety profile of once-monthly Boniva Tablets 150 mg. The adverse events likely to be associated with treatment with Boniva in Study BA18492 are those well-recognized to be associated with the use of bisphosphonates for the treatment or prevention of postmenopausal osteoporosis. These events are addressed in class labeling for bisphosphonates and in labeling for Boniva.

In the Executive Summary of her review (signed November 11, 2008), the primary Medical Reviewer stated the following:

*“No new safety issues emerged from the data provided in the submission. However, the data support upgrading existing warnings. In Study BA18492, among 77 subjects who received ibandronate, safety analysis showed associations between drug intake and*

- *adverse gastrointestinal effects*
- *muscle pain*

*Current labeling describes the associations as derived from postmarketing reports, implying a frequency lower than detectable in clinical trials. Current labeling also states that reports of musculoskeletal pain are “infrequent.” Labeling should be strengthened by removing the words “infrequent” and “postmarketing.”*

#### **Division Director’s Comment**

- *I concur with the recommendation of the primary Medical Reviewer. Revised to-be-approved labeling for Boniva has been strengthened in regard to describing the risk of occurrence of upper gastrointestinal adverse events and musculoskeletal pain in the Warnings and Precautions section of the Package Insert.*

## **9. ADVISORY COMMITTEE MEETING**

The Division determined that an Advisory Committee was not needed to review this application. Ibandronate is not a new molecular entity, the primary protocol-defined efficacy endpoint was achieved, and the clinical data raised no new safety concerns.

## **10. PEDIATRICS**

The Applicant requested a waiver of pediatric studies, as the proposed indication “prevention of osteoporosis in postmenopausal women” does not affect the pediatric population. The Pediatric Review Committee (PeRC) concurred and granted the waiver on October 8, 2008:

*“We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. This drug is used to treat and prevent osteoporosis in postmenopausal women.”*

## **11. OTHER RELEVANT REGULATORY ISSUES**

The Applicant submitted financial disclosure information for all 10 investigators; none had disclosable information.

Site inspections by the Division of Scientific Investigation (DSI) were not requested by the clinical review team.

#### **Division Director’s Comment**

- *There are no unresolved regulatory issues.*

## **12. LABELING**

The trade name Boniva had previously been found to be acceptable by the Division of Medication Errors and Technical Support (DMETS), and it remains the currently used trade

name for this product.

(b) (4)

Although previous Boniva labels had not been approved in the format prescribed by the Physician Labeling Rule (PLR), the label included in this submission was in PLR format. Consults on the proposed label were obtained from the Division of Drug Marketing, Advertising, and Communication (DDMAC). Their comments were incorporated into the label as appropriate. The Division of Risk Management was not consulted regarding Section 17.2 of labeling (FDA-Approved Patient Labeling) because the information contained in Section 17.2 of the revised Package Insert changed only minimally from that contained in the currently approved patient package insert (PPI). The Maternal Health Team provided advice on the Use in Special Populations – Pregnancy section.

The major changes from the previous Boniva label included:

- Addition of clinical trial findings specific to Study BA18492.
- Upgrading of the Warnings and Precautions section of labeling regarding the risk of occurrence of upper gastrointestinal adverse events and musculoskeletal pain.
- Expansion of the Nonclinical Toxicology section in accordance with PLR guidelines.

Final labeling was submitted by the Applicant on November 21, 2008, and was modified slightly on November 24, 2008. The modified labeling of November 24, 2008, was found to be acceptable.

### **13. DECISION/ACTION/RISK BENEFIT ASSESSMENT**

#### **13.1 Regulatory Action**

The Applicant has provided sufficient information for me to conclude that once-monthly Boniva (ibandronate sodium) Tablets 150 mg, when used in accordance with to-be-approved product labeling, will be a safe and effective therapy for the prevention of osteoporosis in postmenopausal women. Once-monthly Boniva (ibandronate sodium) Tablets 150 mg will be approved for the additional indication of “the prevention of osteoporosis in postmenopausal women” based on the (1) safety and efficacy data submitted in support of NDA 21-455/SE1-007, (2) previously reviewed clinical trial safety data and postmarketing safety data for Boniva, and (3) agreed to product labeling,

Both the primary Medical Reviewer (Dr. Furlong, in her review signed November 11, 2008) and the medical Team Leader (Dr. Soule, in her review signed November 25, 2008) have recommended approval of once-monthly Boniva (ibandronate sodium) Tablets 150 mg for the prevention of osteoporosis in postmenopausal women.

#### **13.2 Risk/Benefit Assessment**

The Applicant has demonstrated in a single adequate and well-controlled clinical trial that treatment with once-monthly Boniva Tablets 150 mg was statistically superior to placebo in terms of increasing lumbar BMD in postmenopausal, osteopenic women. The relative treatment

effect, based on percent change from baseline at Month 12 of treatment, was a +4.12% difference in the percent change in lumbar BMD in favor of Boniva (p-value: <0.0001). The safety profile of once-monthly Boniva Tablets 150 mg is acceptable. The types, frequency, and severity of adverse events reported in Study BA18492 are acceptable for a bisphosphonate drug product indicated for the prevention of osteoporosis in postmenopausal women and do not raise any new safety concerns that are not already addressed in class labeling for bisphosphonates. The overall risk/benefit profile for once-monthly Boniva Tablets 150 mg for the prevention of osteoporosis in postmenopausal women is favorable.

### **13.3 Recommendation for Postmarketing Risk Management Activities**

No postmarketing risk management activities are warranted or requested beyond that of the approved product labeling and routine pharmacovigilance monitoring.

### **13.4 Recommendation for other Postmarketing Study Commitments**

No postmarketing study commitments are warranted or requested.

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Scott Monroe  
11/26/2008 06:29:08 PM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	November 24, 2008
<b>From</b>	Lisa M. Soule, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	21-455
<b>Supplement#</b>	SE1-007
<b>Applicant</b>	Roche Pharmaceuticals
<b>Date of Submission</b>	January 28, 2008
<b>PDUFA Goal Date</b>	November 28, 2008
<b>Proprietary Name / Established (USAN) names</b>	Boniva™ Ibandronate sodium tablets
<b>Dosage forms / Strength</b>	Tablet; 150 mg once monthly
<b>Proposed Indication(s)</b>	Prevention of osteoporosis in postmenopausal women
<b>Recommended:</b>	<i>Approval</i>

### 1. Introduction

This efficacy supplement seeks marketing approval for a 150 mg once-monthly dose of ibandronate sodium (hereinafter referred to as Boniva) for prevention of postmenopausal osteoporosis. This strength and dose regimen was approved for the treatment of postmenopausal osteoporosis on March 24, 2005. At that time, labeling was developed that provided for the option of using the 150 mg once monthly dose for prevention as well, in the Dosage and Administration section:

*The recommended dose of BONIVA for the prevention of postmenopausal osteoporosis is one 2.5-mg tablet taken once daily. Alternatively, one 150-mg tablet taken once monthly on the exact same date each month may be considered (see Indications and Usage).*

This permissive labeling was based upon a non-inferiority study that compared the bone mineral density (BMD) in osteoporotic women who took the 2.5 mg daily tablet to those who took the 150 mg monthly tablet, and upon the Applicant's commitment to study the prevention indication (i.e., in an osteopenic population) post-approval. This was not a formal post-marketing commitment.

In the current submission, the Applicant has provided the requested 12-month study evaluating change from baseline in lumbar spine BMD in 160 women at risk for osteoporosis who were randomized to either placebo or the once-monthly 150 mg dose of Boniva.

### 2. Background

#### 2.1 DESCRIPTION OF PRODUCT

Boniva is a bisphosphonate that inhibits osteoclast-mediated bone resorption. Through its affinity for hydroxyapatite in the bone matrix, ibandronate inhibits osteoclast activity and decreases bone resorption and bone turnover. Boniva is currently approved in the U.S. for prevention and/or treatment of postmenopausal osteoporosis (PMO) in three formulations, a

daily 2.5 mg tablet, a monthly 150 mg tablet and a 3 mg solution to be administered intravenously every three months. The latter formulation is indicated only for the treatment of postmenopausal osteoporosis. The 150 mg dose has also been approved for treatment in 88 other countries; the dose has not been approved for the prevention indication in any other country at this time.

Currently, there are four U.S.-approved bisphosphonates for the treatment and/or prevention of PMO, ibandronate (Boniva), alendronate (Fosamax®), zoledronic acid (Reclast®) and risedronate (Actonel®), with several others approved for treatment of non-osteoporosis bone disorders, such as Paget's disease. There are a number of other drug classes approved for the postmenopausal osteoporosis indications, including estrogen with or without a progestin, a selective estrogen receptor modulator (SERM), calcitonin and parathyroid hormone.

## **2.2 REGULATORY HISTORY**

The osteoporosis drug products/indications, including the original NDA and pre-submission interactions relating to this supplement, were previously managed by the Division of Metabolic and Endocrine Products (DMEP). The indications were transferred to the Division of Reproductive and Urologic Products (DRUP, hereinafter referred to as the Division) shortly before submission of this supplement in early 2008.

The initial development of a once-monthly dose for the treatment and prevention indications was discussed with DMEP in December 2001; at that time, the DMEP requested that two trials be conducted, one in a "treatment of PMO" population and one in a "prevention of PMO" population. By DMEP convention, a treatment study enrolled women meeting the BMD criteria for osteoporosis (T score < -2.5), and the primary efficacy endpoint was prevention of fractures. A prevention study enrolled women meeting BMD criteria for osteopenia (T scores < -1.0 but > -2.5), and the efficacy endpoint was change in lumbar spine BMD (i.e., the "prevention" studied was not of fractures but of progression to frank osteoporosis).

DMEP did allow for possible reliance on a single trial that enrolled sufficient numbers of both osteoporotic and osteopenic subjects to perform separate analyses for the two populations. DMEP also recommended conducting a bridging study comparing once-daily to once-monthly Boniva in a treatment population, and proposed to allow preliminary language in the label regarding use of the 150 mg dose for the prevention indication if this study supported approval of the treatment indication.

DMEP met with the Applicant in November 2003, prior to the submission of the efficacy supplement for the once-monthly dose for treatment of PMO. DMEP agreed that, if the treatment indication were approved on the basis of the single 12-month bridging study BM16549, a 12-month placebo-controlled phase 4 study of once-monthly Boniva in the appropriate prevention population would be acceptable to secure preliminary language in the label supporting use for prevention of PMO.

DMEP ultimately approved the treatment indication for the 150 mg dose of Boniva based upon Study BM16549, the 12-month bridging study comparing once-daily 2.5 mg and once-monthly Boniva (both 100 and 150 mg doses were evaluated) for treatment of PMO in March 2005. The approved label did include preliminary language allowing use of the once-monthly 150 mg dose for the prevention indication. The phase 4 study discussed in 2003 was not included as a phase 4 commitment in the Approval letter.

The protocol for the currently submitted study was conducted under IND 50,378 and was reviewed by DMEP medical officers in 2005. Comments were provided to the Applicant concerning expansion of the definition of “postmenopausal,” and addition of some exclusion and withdrawal criteria for safety purposes. The Applicant addressed these in the final protocol.

During the course of the current review, two information requests were submitted to the Applicant, and responses were received to the Division’s questions in each of these.

### **2.3 PRIMARY MEDICAL REVIEWER’S RECOMMENDATION FOR APPROVABILITY**

The primary reviewer, Dr. Lesley Furlong, stated in her review, dated November 6, 2008:

*I recommend approval of the application pending agreement on final labeling.*

#### **Team Leader Comment**

**I concur with Dr. Furlong’s recommendation.**

### **3. CMC/Device**

The primary Chemistry Reviewer, Sharon Kelly, Ph.D., noted that, in this SE1 supplement, no changes had been made regarding manufacture of the drug product, and a microbiology consult was not needed. She made the following recommendations in her review dated October 23, 2008:

*The labeling was provided...PLR coding was reviewed. The Highlights of Prescribing Information, Dosage Forms and Strengths (section 3), Description (section 11), How Supplied/Storage and Handling (section 16), and Patient Information sections of the labeling were reviewed. There are no CMC changes. From a CMC perspective, this Supplement can be Approved.*

#### **3.1 General product quality considerations**

The drug substance and drug product information was reviewed and found acceptable in the original NDA 21-455, and no CMC changes were proposed in this supplement.

#### **3.2 Facilities review/inspection**

No inspections were requested in this review cycle. All facilities used for drug substance and drug product manufacturing for the 150 mg tablets were found to be acceptable as of July 29, 2004, during the review of SE2-001.

### **4. Nonclinical Pharmacology/Toxicology**

The currently proposed dose was approved for treatment of postmenopausal osteoporosis in March 2005; review included pharmacology/toxicology data. No nonclinical studies were submitted in the NDA supplement. The primary Toxicology Reviewer, Lynnda Reid, Ph.D., made the following recommendations in her review dated October 15, 2008:

*Recommendations on approvability: Nonclinical data support approval.*

*Recommendations for nonclinical studies: None*

*Recommendations on labeling: The latest approved label on February 13, 2007, adequately reflects the nonclinical safety/toxicology data for Ibandronate sodium.*

*Recommended changes to Sections 8.1 and 13.2 reflect current recommendations for format and content for animal reproductive and developmental findings for these sections.*

## **5. Clinical Pharmacology/Biopharmaceutics**

The primary Clinical Pharmacology Reviewer, Sandhya Apparaju, Ph.D., stated the following in her review dated July 16, 2008:

*The NDA is acceptable from a Clinical Pharmacology perspective provided an agreement can be reached with the sponsor regarding the labeling language.*

No phase 4 commitments were recommended.

As this dose has already been approved for the treatment of postmenopausal osteoporosis, no new Clinical Pharmacology data were submitted with this supplement. Dr. Apparaju determined that the pharmacokinetics of Ibandronate for the 150 mg tablet, drug-drug interaction and special population dosing issues were adequately addressed during previous NDA reviews for Boniva.

## **6. Clinical Microbiology**

A clinical microbiology consult was not needed according to the primary CMC Reviewer, Dr. Kelly.

## **7. Clinical/Statistical - Efficacy**

### **7.1 OVERVIEW OF CLINICAL PROGRAM**

Clinical data submitted in this NDA are from a single phase 3 safety and efficacy trial, Study BA18492, a 12-month, multicenter, randomized controlled trial that enrolled 160 postmenopausal women aged 45-60 years, at ten U.S. study sites. Subjects were stratified by time since menopause (0.5 - 3 years and > 3 years) and randomized in a 1:1 scheme, with 77 randomized to Boniva and 83 to placebo. Inclusion and exclusion criteria are detailed in Dr. Furlong's review; in general, entry criteria included postmenopausal status (surgically or naturally, according to usual DRUP definitions), with a baseline mean lumbar spine (L2-4) BMD T score of < -1.0 and > -2.5 and baseline proximal femur (total hip, trochanter and femoral neck) BMD T score of > -2.5.

The sample size for this trial was calculated based on results of the phase 3 Boniva prevention trial for the 2.5 mg dose, and was determined to require 66 subjects per treatment arm to provide 90% power to detect a clinically relevant difference in BMD. This number allows for a 20% drop-out rate, to provide 55 evaluable subjects per arm.

The dose regimen employed during the trial included taking the study drug on the same calendar day each month, in the morning following an overnight fast of at least six hours. Subjects were instructed to take the study drug in an upright posture, with an 8 oz. glass of plain water. They were to remain upright and fasting for at least one hour post-dose. All subjects also received 500 mg of calcium and 400 IU of Vitamin D daily.

#### **Team Leader Comment**

**The phase 3 trial dose regimen is consistent with the proposed labeling.**

## 7.2 DEMOGRAPHICS

Table 1 shows the demographics of the safety population.

**Table 1 Demographic and Baseline Characteristics: Safety Population**

	Placebo (N = 83)	Ibandronate 150 mg Monthly (N = 77)
Age, years		
Mean $\pm$ SD	53 $\pm$ 4	54 $\pm$ 4
Range	46 – 60	47 – 60
Body weight, kg (mean $\pm$ SD)	71 $\pm$ 16	70 $\pm$ 15
Body mass index, kg/m <sup>2</sup> (mean $\pm$ SD)	27 $\pm$ 6	27 $\pm$ 5
Time since menopause, % pts		
0.5 to 3 years	59	64
> 3 years	41	36
Time since menopause (years)		
Mean $\pm$ SD	5.5 $\pm$ 5.8	5.3 $\pm$ 6.0
Median	2.4	2.3
Range	0.5 – 28	0.7 – 25
Postmenopausal HRT, [No. (% pts)]	26 (31)	21 (27)
Months of use (median)	24.0	48.0
Range	2 – 336	2 – 240
Mean BMD at baseline (g/cm <sup>3</sup> )		
Lumbar spine	0.91	0.91
Total hip	0.87	0.88
Trochanter	0.64	0.64
Femoral neck	0.73	0.74
Mean BMD T-scores at baseline (g/cm <sup>3</sup> )		
Lumbar spine	-1.57	-1.58
Total hip	-0.59	-0.49
Trochanter	-0.65	-0.59
Femoral neck	-1.08	-0.99
Median serum CTX at baseline (ng/mL)	0.56	0.48

Source: Applicant's Table 1, page 11 of Clinical Overview.

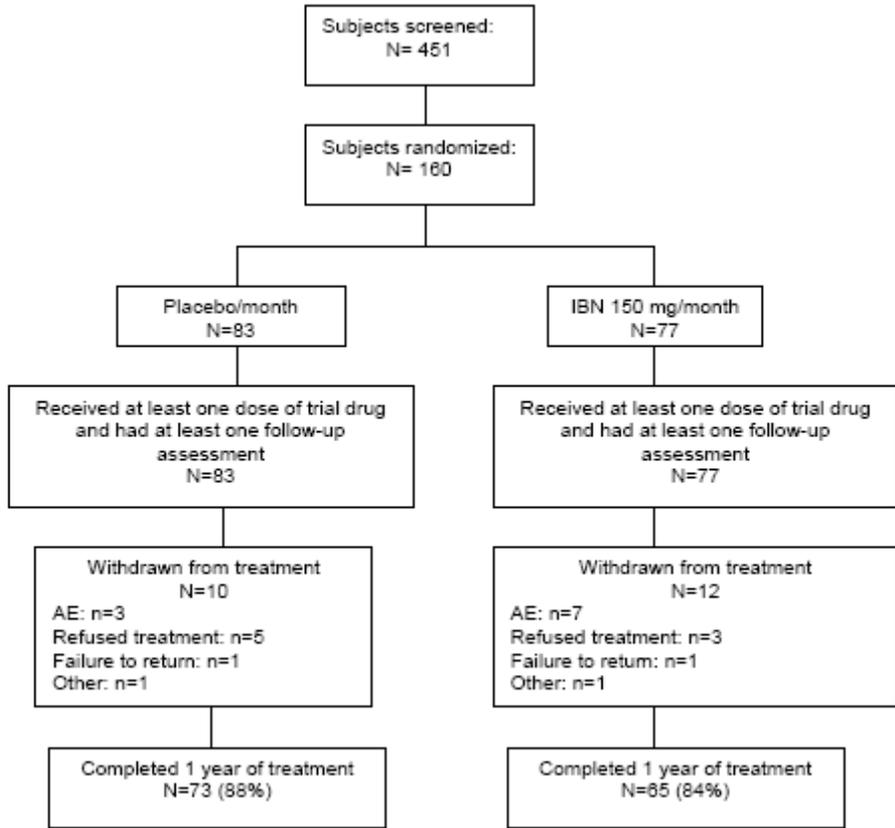
### Team Leader Comments

- The two treatment arms are very similar on baseline BMD measures. The time since menopause, a likely risk factor for osteoporosis, is also very similar, as is body mass index (BMI).
- Other risk factors for osteoporosis, such as smoking and family history of osteoporotic fractures, are not shown in this table, but were also similar in the treatment arms.
- Although not included on this table, treatment arms were also similar regarding race/ethnicity, with both being almost exclusively Caucasian (95% and 96%, respectively, in the Boniva and placebo groups), with no more than 2 subjects per arm described as Black, Asian or "Other." Hispanics comprised 26% and 25% respectively.

## 7.3 DISPOSITION OF SUBJECTS

A total of 451 women were screened for the study, with 160 randomized. Similar proportions in each arm withdrew from the study prior to completion (see Table 2). All randomized subjects took at least one dose of study drug (comprising the safety population), and 73 placebo subjects and 65 Boniva subjects completed one year of treatment.

**Table 2 Disposition of Subjects**



Source: Applicant's Figure 1, page 44, Final Study Report

A total of 22 women from the safety population discontinued prematurely for the reasons described in Table 3.

**Table 3 Reasons for Discontinuation (Safety Cohort)**

	Placebo N (%of safety population)	Boniva N (%of safety population)
<b>Safety Population</b>	83 (100)	77 (100)
<b>Completed study</b>	73 (88)	65 (84)
<b>Did not complete</b>	10 (12)	12 (16)
<b>Reason for discontinuation</b>		
<b>Adverse event</b>	3 (3.6)	7 (9.1)
<b>Refused treatment</b>	5 (6.0)	3 (3.9)
<b>Failure to return</b>	1 (1.2)	1 (1.3)
<b>Other</b>	1 (1.2)	1 (1.3)

Source: Applicant's Table 4, page 45, Final Study Report

**Team Leader Comments**

- **The ten subjects withdrawn due to adverse events (AEs) are further discussed in Section 8.1.1.**
- **No case report forms were submitted for any subjects other than the 10 who discontinued due to AEs. Thus, there is limited information regarding the specific reasons for withdrawal outside of AEs.**
- **The eight subjects withdrawn due to “refused treatment” were described as “withdrew” under Reason for Withdrawal, with no further explanation provided. Placebo subjects withdrew on Days 140 – 233, while Boniva subjects withdrew on Days 126 – 301.**
- **No further explanation was provided for the two subjects who “failed to return.”**
- **The two subjects withdrawn due to “other” included a placebo subject whose job was relocated out of state, and a Boniva subject who was out of the country.**
- **Loss to follow-up of about 1% of the population in each arm is acceptable.**

**7.4 EFFICACY FINDINGS**

**7.4.1 Assessment of Efficacy**

The primary efficacy endpoint was the relative (%) change from baseline in mean lumbar spine (L2-4) BMD at 12 months of treatment. Pre-specified secondary endpoints included:

- Absolute change from baseline in mean lumbar BMD at month 12
- Relative and absolute change from baseline in mean BMD in total hip, trochanter and femoral neck at month 12
- Percent responders, defined as
  - Subjects with mean lumbar spine BMD  $\geq$  baseline at month 12
  - Subjects with proximal femur BMD (total hip, trochanter and femoral neck )  $\geq$  baseline at month 12
  - Subjects with both mean lumbar spine and proximal femur BMD  $\geq$  baseline at month 12
- Relative and absolute change from baseline in the serum marker of bone resorption, C-telopeptide of  $\alpha$ -chain of type I collage (CTX) at months 3, 6, and 12

The BMD endpoints were measured by a single dual energy X-ray absorptiometry (DEXA) scan of the lumbar spine and proximal femur at baseline and month 12. The month 12 DEXA was read at a central facility (b) (4). The central reading site could request repeat 12 month scans if the original was judged unsuitable (affected by a fracture, osteoarthritic process or scanning artifact that jeopardized accurate BMD assessment) or if it showed significant bone loss (lumbar spine BMD decrease of > 5%, hip BMD of > 7%).

The primary analysis was an ANOVA that included treatment arm, baseline lumbar BMD, and time since menopause stratum as independent factors. A two-tailed test was performed, at an alpha of 0.05. The intent-to-treat (ITT) population, defined as all subjects who took at least one dose of study medication, and had baseline and at least one follow-up evaluation data point was the primary efficacy population.

**Team Leader Comment**

**The primary endpoint was found to be acceptable in the protocol review by DMEP.**

Subjects who withdrew from the study were to have a complete final examination; however, no “early termination” visit to obtain the efficacy endpoints was planned. Subjects who discontinued within two months of the end of treatment were encouraged to return for the BMD scan.

#### 7.4.1.1 Primary Efficacy Analysis

The analysis of the primary efficacy endpoint in the ITT population yielded statistically significant result favoring Boniva in the prevention of PMO. The change from baseline in lumbar spine BMD reported by the Applicant for subjects treated with Boniva as compared to those treated with placebo was significant at a  $p < 0.0001$  level, and the overall treatment effect was 4.12. This was confirmed by the FDA statistician (see Table 4). The “raw mean” data included BMD measurements in which unevaluable and/or fractured vertebrae were identified; while “adjusted” mean data excluded such measurements.

**Table 4 Primary ANOVA of Relative Change from Baseline at Month 12 in Lumbar BMD**

	<b>Placebo</b> (n=83)	<b>Boniva</b> (n=77)
<b>N</b>	70 (86%)	68 (88%)
<b>Raw mean (S.D.)</b>	-0.43 (3.49)	3.58 (3.48)
<b>Adjusted mean</b>	-0.39	3.73
<b>S.E.</b>	0.41	0.42
<b>Treatment effect</b>	--	4.12
<b>95% CI</b>		2.96, 5.28
<b>P-value</b>		<0.0001

Source: Based on Table 2 in review by FDA statistician, Stella Grosser, Ph.D., dated November 14, 2008

#### Team Leader Comment

**The Applicant met the protocol-defined primary efficacy endpoint of percent change from baseline in Month 12 lumbar spine BMD.**

#### Statistician’s Conclusion

The statistical reviewer, Stella Grosser, Ph.D., analyzed the data and conducted sensitivity analyses to account for the subjects who terminated the trial prematurely. To do this, she assigned all Boniva subjects who withdrew the mean change from baseline in lumbar spine BMD that was observed in the placebo group, and did the converse for the early withdrawals in the placebo group. The treatment effect remained large (2.9). She made the following recommendation in her review dated November 14, 2008:

*There is a statistically significant difference, in favor of IBN [ibandronate], in relative change from baseline in the mean BMD of the lumbar spine at 12 months. Sensitivity analysis of the primary endpoint, as well as analysis of the secondary endpoints, further support the efficacy of IBN 150 mg once monthly in the prevention of bone loss in osteopenic women.*

#### Team Leader Comment

**Dr. Grosser’s calculation of the primary efficacy results confirms that submitted by the Applicant. Her sensitivity analyses provide further support for the efficacy of 150 mg Boniva for the prevention indication.**

#### 7.4.1.2 Secondary Efficacy Analysis

The Applicant conducted a number of analyses of secondary efficacy endpoints, including:

- Absolute change from baseline in mean lumbar BMD at month 12: the mean absolute change was  $-0.004 \text{ g/cm}^2$  in the placebo group and  $0.032 \text{ g/cm}^2$  in the Boniva group, with non-overlapping confidence intervals
- Relative and absolute change from baseline in mean BMD in total hip, trochanter and femoral neck at month 12: all showed greater change in the Boniva group
- Relative change from baseline in the serum marker of bone resorption, C-telopeptide of  $\alpha$ -chain of type I collage (CTX) at months 3, 6, and 12: showed a greater decrease in CTX at each time point (indicating a decrease in bone resorption and overall bone turnover) for the Boniva arm, with non-overlapping confidence intervals
- Responder analyses, defined as:
  - Subjects with mean lumbar spine BMD  $\geq$  baseline at month 12: odds ratio on being a responder of 12.5 in favor of Boniva
  - Subjects with proximal femur BMD (total hip, trochanter and femoral neck )  $\geq$  baseline at month 12: odds ratio of 8.6 in favor of Boniva
  - Subjects with both mean lumbar spine and proximal femur BMD  $\geq$  baseline at month 12: odds ratio of 13.8 in favor of Boniva

The Applicant also analyzed the primary efficacy endpoint for two strata: women 0.5 to 3 years since menopause and women  $> 3$  years since menopause. Boniva demonstrated a statistically significant treatment as compared to placebo effect in both strata.

Dr. Furlong conducted exploratory analyses of clinical endpoints – mean change in baseline height at Month 12 and number of clinical fractures. There was a slight gain in mean height (no change in median height) among placebo subjects and slight loss in mean and median height in Boniva subjects; however, the confidence intervals overlapped. Each group had two non-vertebral fractures, and no vertebral fractures were reported in either group.

#### Team Leader Comments

- **The Applicant's secondary efficacy analyses and sensitivity analyses of the primary endpoint supported efficacy of Boniva.**
- **The lack of efficacy on the non-vertebral fracture endpoint was also demonstrated in the clinical trial supporting the treatment indication for the 2.5 mg dose, although that trial did demonstrate efficacy in reduction of vertebral fractures in the Boniva arm.**

#### 7.4.2 Overall Assessment of Efficacy

The Applicant has submitted an acceptable clinical trial database supporting efficacy for this expanded indication of prevention of PMO for an approved dose and dose regimen. The Applicant met the primary efficacy endpoint of change from baseline in lumbar spine BMD, and secondary endpoint analyses were also supportive. Although not a pre-specified endpoint, there appears to be no efficacy benefit for Boniva in preventing non-vertebral fractures; these occurred in two subjects in each group (all were traumatic fractures). No vertebral fractures occurred in either group; however, the study was not powered to show a difference in the risk of vertebral fractures.

## 8. Safety

### 8.1 SAFETY FINDINGS

This review of the safety of Boniva is based on data from the 12-month safety and efficacy trial. The safety population in Study BA18492 included 160 women (77 Boniva, 83 placebo) who took at least one dose of study medication, or 100% of all enrolled subjects.

#### 8.1.1 Deaths and Serious Adverse Events

There were no deaths in the clinical trial. There were three SAEs reported by Boniva-treated subjects in the phase 3 trial, and one in a placebo-treated subject, as displayed in Table 5; all were judged to be unrelated to treatment.

**Table 5 Serious Adverse Events in Study BA18492**

Subject #	Treatment Arm	SAE MedDRA Term (Discussion)	Discontinued from study	Applicant assessment of causality	Reviewer assessment of causality
1015	Boniva	Pyelonephritis (history of bladder prolapse)	No	Unrelated	Unrelated
1367	Boniva	Upper limb fracture (high impact trauma, following fall from a ladder)	Yes	Unrelated	Unrelated
1376	Placebo	Cellulitis (post-traumatic hand infection)	No	Unrelated	Unrelated
1380	Boniva	Chest pain (non-cardiac, diagnosed as GERD)	Yes	Unrelated	Unrelated

Source: Based on Applicant's Listing ae01\_s, pp 428-9 of final study report

#### Team Leader Comment

**One additional SAE for a Boniva subject was originally listed – Helicobacter pylori infection in Subject #1244. However, following database lock, the investigator indicated to the Applicant that classification of this AE as “serious” had been in error. While this may not indeed meet the criteria for a SAE, H. pylori infection supports a presumptive diagnosis of a gastrointestinal ulcer**

A total of seven subjects (9.1%) in the Boniva arm, and three subjects (3.6%) in the placebo arm discontinued the trial due to adverse events (AEs). Adverse events leading to study discontinuation are listed in Table 6.

**Table 6 AEs Leading to Study Discontinuation in the Safety Population**

Subject #	Treatment Arm	Description
1012	Boniva	Gastroesophageal reflux disease (GERD)
1129	Placebo	Periarthritis
1188	Placebo	Heartburn
1192	Boniva	Severe muscle pain
1249	Boniva	Weight increase (4#)
1364	Placebo	GERD
1367	Boniva	Traumatic upper limb fracture
1370	Boniva	Flu-like symptoms (headache, myalgia, arthralgia)
1380	Boniva	Chest pain (GERD)
1503	Boniva	Nausea, upset stomach, cramps, fatigue

Source: Based on Applicant's Table 45, pp 87 of final study report

**Team Leader Comments**

- **AEs leading to discontinuation relating to GERD occurred more frequently in Boniva than placebo subjects (2 vs. 1). However, an additional placebo subject experienced "heartburn," which may represent a similar disorder.**
- **Severe muscle pain leading to discontinuation was also more common in Boniva-treated subjects (2 vs. 0 in the placebo group). Each of these subjects experienced the symptoms on multiple occasions following her monthly dose of Boniva (one over four months, one over seven months).**
- **The Applicant considered three of the Boniva subjects to have suffered "flu-like symptoms" but categorized two of these as treatment-related.**

Other AEs of significance included clinical fractures; these occurred in two subjects in each treatment arm (two placebo subjects [Subjects #1364 and 1533] had foot fractures; one Boniva subject [Subject # 1130] had a Colles fracture of her radius, and one [Subject #1367] had a rib and an radial head fracture). All were associated with trauma; none were attributed to osteopenia.

**8.1.2 Other Adverse Events**

AEs occurring in > 2% of the Boniva subjects and in a higher proportion than in the placebo arm in the safety population are listed in Table 7.

**Table 7 Common Adverse Events (≥ 2% of Safety Population and More Common in Boniva Arm)**

MedDRA Preferred Term	Placebo N = 83 n (%)	Boniva N = 77 n (%)
Arthralgia	8 (9.6)	12 (15.6)
Myalgia	2 (2.4)	5 (6.5)
Nausea	3 (3.6)	5 (6.5)
Pain in Extremity	5 (6.0)	5 (6.5)
Influenza-like illness	0	4 (5.2)
Hypercholesterolemia	1 (1.2)	4 (5.2)
Insomnia	1 (1.2)	4 (5.2)
Dental caries	3 (3.6)	4 (5.2)
GERD	3 (3.6)	4 (5.2)
Dyspepsia	4 (4.8)	4 (5.2)
Headache	4 (4.8)	4 (5.2)
Depression	1 (1.2)	3 (3.9)
Musculoskeletal pain	1 (1.2)	3 (3.9)
Fatigue	2 (2.4)	3 (3.9)
Diabetes mellitus	0	2 (2.6)
Muscle strain	0	2 (2.6)
Pyelonephritis	0	2 (2.6)
Abdominal pain lower	1 (1.2)	2 (2.6)
Abdominal pain upper	1 (1.2)	2 (2.6)
Anxiety	1 (1.2)	2 (2.6)
Hypoesthesia	1 (1.2)	2 (2.6)
Vertigo	1 (1.2)	2 (2.6)
Weight increased	1 (1.2)	2 (2.6)
Neck pain	2 (2.4)	2 (2.6)

Source: Based on Applicant's Table 42, p 83 of final study report

**Team Leader Comments**

- **Grouping related terms, it can be seen that the Boniva arm experienced a higher frequency of musculoskeletal AEs (arthralgia + myalgia + pain in extremity + influenza-like illness + musculoskeletal pain + muscle strain + neck pain); these occurred in 33 (43%) of Boniva subjects as compared to 18 (22%) of placebo subjects. Even if some subjects experienced more than one of these events (i.e., if they are not independent events), there is a marked excess among Boniva-exposed subjects.**
- **Similarly, looking at gastrointestinal AEs (nausea + GERD + dyspepsia + abdominal pain lower + abdominal pain upper), 17 Boniva subjects (22%) experienced such AEs, compared to 12 placebo subjects (14%).**

The primary medical reviewer undertook a series of analyses further to evaluate the signals of musculoskeletal pain and gastrointestinal (GI) AEs. Regarding musculoskeletal pain, Dr. Furlong elucidated the occurrence of these AEs in two subjects who experienced recurrence of these symptoms on multiple occasions following the monthly dosing of Boniva (after each of four doses for one subject, and after each of seven doses for the other). This is nicely demonstrated in Dr. Furlong's review, Tables 4 and 5. Such a challenge/rechallenge

pattern suggests that the AE is drug-related. Dr. Furlong also assessed the locations of musculoskeletal AE reports and found that placebo subjects tended to report specific muscle groups (back, knee), while Boniva subjects reported generalized myalgias.

Gastrointestinal complaints such as GERD are common among menopausal women<sup>1</sup>, but Dr. Furlong further explored the time-relatedness of AEs by assessing those AEs that occurred within five days after dosing with study drug (the approximate  $T_{1/2}$  of Boniva, and the approximate time at which calcium nadirs following IV Boniva administration<sup>2</sup>). She noted an imbalance in AE frequency, with more AE reports in Boniva subjects (24) than in placebo subjects (7) within five days after the first dose of study drug, and within five days after any dose of study drug (Boniva: 86 AEs in 33 subjects, placebo: 24 AEs in 17 subjects). The majority of the AE reports involved the musculoskeletal or GI systems.

The Applicant evaluated clinical chemistry and hematology labs at screening, and Months 3, 6 and 12; the latter samples were drawn at likely trough ibandronate levels. There were no clinically relevant changes in mean lab values, and no subjects were withdrawn due to abnormal labs. The most relevant chemistry value is calcium level; the mean change from baseline ranged from -0.01 to -0.04 mmol/L in the Boniva arm, and from -0.01 to -0.05 mmol/L in the placebo arm.

The Applicant assessed weight and height, but no other vital signs. A product that is efficacious in prevention of vertebral fractures would be expected to show a lesser decrease in height than placebo. As noted in Section 7.4.1.2, this was not found for Boniva, which had a slight decrease in mean height, as compared to a slight increase for placebo. Weight changes on Boniva were minimal, and similar to that seen in the placebo group.

### **8.1.3 Safety Update**

A 120-day Safety Update Report was not submitted; the Applicant indicated on May 22, 2008 that there were no ongoing studies, nor any additional safety data accrued from Study BA 18492 subsequent to the initial submission.

### **8.1.4 Postmarketing Safety Findings**

As an approved product, periodic adverse drug event reports (PADERs) are submitted for Boniva annually. These have previously been reviewed in DMEP; the most recently submitted, July 14, 2008, was reviewed by the DRUP primary medical reviewer. The Applicant indicates that no labeling changes have been initiated based on postmarketing surveillance findings.

On October 1, 2007, FDA issued an Early Communication about an ongoing safety review of bisphosphonates, with regard to possible increased risk of atrial fibrillation. This concern arose from an article and letter to the editor published in the *New England Journal of Medicine*, describing two studies that showed increased rates of serious atrial fibrillation among women treated with zoledronic acid or alendronate as compared to women taking

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<sup>1</sup> Infantino, M. The prevalence and pattern of gastroesophageal reflux symptoms in perimenopausal and menopausal women. *Amer Acad Nurse Pract* 20: 266-72, 2008

<sup>2</sup> Pecherstorfer M, Ludwig H, Schlosser K, et al. Administration of the bisphosphonate ibandronate by intravenous bolus injection. *J Bone and Min Res* 11:587, 1966

placebo. FDA reviewed placebo-controlled clinical trial data on almost 20,000 patients treated with bisphosphonates and over 18,000 patients treated with placebo, for durations ranging from six months to three years. FDA issued an update on November 12, 2008 indicating that no clear association of bisphosphonate exposure with atrial fibrillation had been observed, not was there any dose- or duration-related increase in risk of atrial fibrillation demonstrated. FDA continues to monitor postmarketing reports of atrial fibrillation in bisphosphonate users, and is exploring the feasibility of conducting additional epidemiologic studies.

### **8.1.5 Overall Assessment of Safety Findings**

This new safety and efficacy study for Boniva does not provide any new safety signals. Several events previously labeled as infrequent and occurring postmarketing, musculoskeletal pain and GI effects, occurred in this small trial, and Dr. Furlong's elegant analysis of concordance with dosing and challenge/rechallenge demonstrate their drug-relatedness. The labeling should be upgraded to reflect the identification of these AEs in a placebo-controlled trial, and their relative frequency.

## **9. Advisory Committee Meeting**

The Division determined that an Advisory Committee was not needed to review this application, as it was not a new molecular entity and raised no new safety concerns.

## **10. Pediatrics**

The Applicant requested a waiver of pediatric studies, as the proposed indication does not affect the pediatric population. The Pediatric Review Committee (PeRC) concurred and granted the waiver on October 8, 2008:

*We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. This drug is used to treat and prevent osteoporosis in postmenopausal women.*

## **11. Other Relevant Regulatory Issues**

The Applicant submitted financial disclosure information for all 10 investigators; none of whom had disclosable information.

Site inspections by the Division of Scientific Investigation (DSI) were not requested. Although one site enrolled 24% of all subjects, had more favorable than average change in BMD and had a lower than average rate of adverse events, consultation with DSI revealed that the site had a previous acceptable inspection in 2004 with respect to another Ibandronate study.

## **12. Labeling**

The trade name Boniva has already been found to be acceptable.

Carton and container labeling was reviewed and found not to be revised from that already approved.

The Boniva label was submitted in the format prescribed by the Physician Labeling Rule (PLR). Although previous Boniva labels have not been approved in PLR format, other

bisphosphonates for postmenopausal osteoporosis have developed PLR labeling (Actonel). Consults on the proposed label were obtained from the Division of Drug Marketing, Advertising and Communication. Their comments were incorporated into the label as appropriate. The Division of Risk Management was not consulted regarding Section 17.2 of labeling (FDA-Approved Patient Labeling) because the information contained in Section 17.2 of the revised Package Insert changed only minimally from what is contained in the currently approved patient package insert (PPI) for the Boniva label. The Maternal Health Team provided advice on the Use in Special Populations – Pregnancy section.

The major changes from the previous Boniva label include:

- Addition of clinical trial findings specific to Study BA18492
- Upgrading of Adverse Reaction labeling regarding musculoskeletal pain and GI effects
- Expansion of the Nonclinical Toxicology section in accord with PLR guidelines

Labeling submitted by the Applicant on November 21, 2008 was found to be acceptable.

## **13. Recommendations/Risk Benefit Assessment**

### **13.1 Recommended Regulatory Action**

I recommend that Boniva in the 150 mg dose and once-monthly dose regimen be approved for the indication “prevention of osteoporosis in postmenopausal women.”

### **13.2 Risk Benefit Assessment**

The one-year clinical trial demonstrated efficacy for the once-monthly 150 mg dose of Boniva in prevention of PMO, as assessed by an increase from baseline in lumbar spine BMD. The safety profile does not differ from that already demonstrated for this approved product, although adverse drug reactions of musculoskeletal pain and GI effects should be described with upgraded labeling. With appropriate labeling, I believe that once-monthly Boniva 150 mg has demonstrated safety and efficacy acceptable to allow approval for marketing for the indication of prevention of osteoporosis in postmenopausal women.

### **13.3 Recommendation for Postmarketing Risk Management Activities**

No postmarketing risk management activities beyond labeling are recommended.

### **13.4 Recommendation for other Postmarketing Study Commitments**

No postmarketing studies are recommended.

### **13.5 Recommended Comments to Applicant**

None.

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Lisa Soule  
11/25/2008 01:57:55 PM  
MEDICAL OFFICER

Scott Monroe  
11/25/2008 02:05:54 PM  
MEDICAL OFFICER

I concur with Dr. Soule's recommendation that "Boniva in  
the 150 mg dose and once-monthly dose regimen  
be approved for the indication prevention of osteoporosis  
in postmenopausal women."

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA  
Submission Number 21-455  
Submission Code SE1-007

Letter Date 25-Jan-2008  
Stamp Date 28-Jan-2008  
PDUFA Goal Date 28-Nov-2008

Reviewer Name Lesley-Anne Furlong  
Review Completion Date 06-Nov-08

Established Name Boniva  
(Proposed) Trade Name ibandronate sodium tablets  
Therapeutic Class bisphosphonate  
Applicant Roche

Priority Designation S

Formulation tablets  
Dosing Regimen a single tablet taken monthly  
Indication prevention of osteoporosis  
Intended Population postmenopausal women

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## 1 Executive Summary

### 1.1 Recommendation on Regulatory Action

I recommend approval of the application pending agreement on final labeling.

Ibandronate 150 mg monthly is approved for the treatment and prevention of osteoporosis in postmenopausal women. The current submission contains the results of Study BA18492, performed to obtain final labeling for the prevention indication. The submission also updates the package insert to the “Physician Labeling Rule” (PLR) format.

The applicant demonstrated efficacy of ibandronate 150 mg monthly for the prevention of postmenopausal osteoporosis by meeting the pre-specified endpoint of Study BA18492: the mean percentage change from baseline in lumbar bone mineral density (BMD) after one year of treatment was 3.73% for 68 subjects treated with ibandronate, compared with -0.39% for 70 subjects treated with placebo. The p-value for the comparison was less than 0.0001.

No new safety issues emerged from the data provided in the submission. However, the data support upgrading existing warnings. In Study BA18492, among 77 subjects who received ibandronate, safety analysis showed associations between drug intake and

- adverse gastrointestinal effects
- muscle pain

Current labeling describes the associations as derived from postmarketing reports, implying a frequency lower than detectable in clinical trials. Current labeling also states that reports of musculoskeletal pain are “infrequent.” Labeling should be strengthened by removing the words “infrequent” and “postmarketing.”

### 1.2 Recommendation on Postmarketing Actions

Postmarketing surveillance is ongoing for the product and should continue.

### 1.3 Summary of Clinical Findings

#### *1.3.1 Brief Overview of Clinical Program*

Study BA18492 was a double-blind, randomized, controlled, ten-center, U.S. study comparing ibandronate to placebo. Group A received ibandronate 150 mg taken orally once monthly and Group B received matching placebo. The primary endpoint, bone mineral density at the lumbar spine, was measured after one year of therapy. Subjects received 12 months of treatment and were followed for an additional 15 days. The study enrolled 160 postmenopausal women with osteopenia; 83 women received placebo and 77 women received ibandronate. The safety analysis included all subjects who received treatment. The efficacy analysis included all subjects who provided bone mineral density (BMD) data at 12 months.

### *1.3.2 Efficacy*

Study BA18492 supported the efficacy of ibandronate in prevention of osteoporosis in postmenopausal women by meeting the pre-specified efficacy endpoint. The mean percentage change from baseline in lumbar BMD density after one year of treatment was 3.73% for 68 subjects treated with ibandronate, compared with -0.39% for 70 subjects treated with placebo. The p-value for the comparison was less than 0.0001.

The applicant also provided analyses of responders, subgroups, per protocol groups, and BMD at non-vertebral sites, all of which were supportive. On the other hand, changes in mean and median height did not support efficacy. Height changes, which were not summarized by the applicant, could be calculated from the datasets. The ibandronate group had a small loss in mean (-0.6 cm) and median height (-1.0cm), whereas the placebo group had a small increase in mean height (0.7 cm) and no change in median height. However, the 95% confidence intervals around the estimates of change in height overlapped. The incidence of fractures, a meaningful clinical endpoint, was no different between treatment groups. No vertebral fractures were detected in either group, and two non-vertebral fractures were detected in each group.

By itself, Study BA18492 would be insufficient to support approval for prevention of osteoporosis. Bone mineral density is a surrogate endpoint that does not always link to a meaningful clinical outcome. However, previous studies of ibandronate provided support for prevention of vertebral fracture in postmenopausal women using ibandronate. A three-year placebo-controlled study of 2,946 postmenopausal women with a history of vertebral fractures showed that a daily dose of 2.5 mg ibandronate reduced the risk of vertebral fractures by approximately 50%. Furthermore, a one-year study linked the 2.5 mg daily dose to the 150 mg monthly dose of ibandronate by showing that the 150 mg monthly dose of ibandronate was non-inferior to the 2.5 mg daily dose in percent change from baseline in lumbar spine BMD. The study involved 1,602 postmenopausal women with osteoporosis. Taken together, the results of all three studies provide reasonable support for the efficacy of ibandronate in preventing osteoporosis in postmenopausal women.

Study BA18492 was consistent with previous larger studies of ibandronate: it provided no evidence that treatment with ibandronate prevented non-vertebral fractures. Two subjects in the placebo group and two subjects in the ibandronate group had non-vertebral fractures during treatment.

### *1.3.3 Safety*

Study BA18492 added 77 subjects treated with ibandronate and 83 subjects treated with placebo to the safety database for ibandronate. The planned exposure for Study BA18492 was one year. The actual mean duration of treatment was 11 months for the ibandronate subjects and 11.2 months for the placebo group.

Although no new safety signals emerged in Study BA18492, the safety data support upgraded labeling with respect to musculoskeletal and gastrointestinal effects.

Current labeling indicates that that gastrointestinal effects and muscle pain are a “postmarketing experience,” implying a frequency that is lower than detectable in clinical trials. Labeling also states that reports of musculoskeletal pain are “infrequent.” Labeling should be strengthened by removing the words “infrequent” and “postmarketing.” The review that follows supports a connection between gastrointestinal symptoms, muscle pain, and ibandronate through analysis of

- adverse events that occurred within five days of dosing
- challenge-rechallenge data
- comments of investigators related to subjects who discontinued therapy

Among 77 women treated with ibandronate, three had symptoms described as “severe muscle pain,” “myalgia,” or “cramps,” along with other symptoms that were severe enough to result in discontinuation of treatment. Two of the three women provided 11 instances of challenge-rechallenge (Table 4, Table 5). The pattern seen with challenge-rechallenge was onset within one day of dosing, followed by persistence for four to eight days. Among 83 women treated with placebo, no one discontinued treatment for muscle pain.

Hypocalcemia is a plausible reason for the muscle complaints because myalgia is a symptom of hypocalcemia, and because the time course for myalgia is similar to the expected time course reported in the literature for hypocalcemia related to ibandronate. Whether hypocalcemia occurred in the subjects who developed myalgia in Study BA18492 is unknown because calcium levels were not obtained during the myalgia events.

Regarding gastrointestinal adverse events, support for strengthening labeling came from one ibandronate-treated subject who may have had an ulcer, and analysis of adverse events that occurred within five days of dosing. Evidence for an ulcer in one of 77 subjects treated with ibandronate came from an adverse event described as “H. pylori,” followed by therapy with Prevpac, a combination product indicated for the treatment of *Helicobacter pylori* infection and duodenal ulcer disease. Analyses of adverse events that occurred within five days of dosing provided further support for strengthening labeling related to both gastrointestinal adverse events and muscle pain (Table 13, Table 15).

No deaths were reported during the study. Three serious adverse events (SAEs) were reported among subjects treated with ibandronate (pyelonephritis, gastroesophageal reflux disease, and a fall from a ladder resulting in multiple fractures). One SAE was reported for a subject receiving placebo (cellulitis).

#### *1.3.4 Dosing Regimen and Administration*

Subjects took study drug on the same calendar day each month, in the morning after an overnight fast of six hours or more, in an upright position, and with an 8 ounce glass of plain water. After

dosing, subjects stayed upright and fasted for at least 60 more minutes. Only water was allowed during the fasting periods.

Dose selection was based on the results of a previous study, Study BM16549, which was the basis of approval of the 150 mg dose of ibandronate for the treatment of osteoporosis. In Study BM16549, the increase in lumbar spine BMD in the 150 mg treatment group was superior to that in the 2.5 mg daily group and the 100 mg monthly treatment group.

### *1.3.5 Drug-Drug Interactions*

No metabolic drug-drug interactions appear on current labeling. Ibandronate is eliminated unchanged by the kidneys. Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system. Ibandronate has a low oral bioavailability that is decreased further by intake of food, medication, or liquid (except for water) within 60 minutes of ibandronate intake.

### *1.3.6 Special Populations*

The treatment indications for ibandronate are limited to postmenopausal women. Current labeling recommends

- No dose adjustment for patients with hepatic impairment because ibandronate is not metabolized by the liver
- No dose adjustment for patients with mild or moderate renal impairment, but ibandronate “is not recommended for use in patients with severe renal impairment”
- No dose adjustment in elderly

## **2 INTRODUCTION AND BACKGROUND**

### **2.1 Product Information**

Boniva is a bisphosphonate that inhibits osteoclast-mediated bone resorption. It is approved in the United States in three formulations:

- Boniva 2.5 mg, one tablet daily (approved May 16, 2003)
- Boniva 150 mg, one tablet monthly (approved May 24, 2005)
- Boniva injection, solution, 3 mg, administered intravenously every three months (approved Jan. 6, 2006)

All approved formulations prevent vertebral fractures in postmenopausal women. However, none of the formulations has been shown to prevent non-vertebral fractures in postmenopausal women.

The intravenous formulation is indicated for the treatment of osteoporosis in postmenopausal women. The tablet formulations are indicated for the treatment and prevention of osteoporosis in postmenopausal women. When FDA approved the 150 mg tablet formulation, FDA allowed the prevention language in labeling based on the results of a study comparing the effects of the 2.5 mg and 150 mg formulations on bone mineral density in women with osteoporosis, and based on the applicant's commitment to study the prevention indication postmarketing. The current submission contains the study report that fulfills the commitment.

### **2.2 Currently Available Treatment for Indications**

A number of drug options are approved for prevention of postmenopausal osteoporosis, including

- bisphosphonates, for example, Boniva (as a daily dose formulation), Actonel, and Fosamax
- estrogen-containing products, for example, Climara, Prempro, and Activella
- the estrogen receptor modulator, raloxifene

### **2.3 Availability of Proposed Active Ingredient in the United States**

Ibandronate is approved in the United States as

- Boniva tablets, 2.5 mg taken daily or 150 mg taken once monthly
- Boniva injection, 3 mg dose given intravenously every three months

### **2.4 Important Issues with Pharmacologically Related Products**

Bisphosphonates given orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcers. Labeling states that Boniva is not to be taken in

women with hypocalcemia. Bisphosphonates are also used to treat hypercalcemia secondary to metastatic cancer, and may cause hypocalcemia. There have been reports of osteonecrosis, primarily in the jaw, in patients treated with bisphosphonates. Additionally, labeling states that musculoskeletal pain has been reported postmarketing.

## **2.5 Presubmission Regulatory Activity**

The presubmission regulatory activity was managed by FDA's Division of Metabolic and Endocrine Products. The indication was transferred to FDA's Division of Reproductive and Urologic Products shortly before submission of the supplement that is the subject of this review.

In May 2003, FDA approved Boniva 2.5 mg oral daily tablets for the prevention and treatment of postmenopausal osteoporosis. At the time of approval the applicant had a monthly 150 mg dosage formulation under development.

In 2002, the applicant requested a special protocol assessment for a proposed single Phase 3 protocol for the monthly 150 mg formulation. In its response, the FDA recommended a trial for the treatment indication and a trial for the prevention indication. However, the FDA stated that "...it would be reasonable to first conduct a BMD bridging study comparing once-daily ibandronate to once-monthly ibandronate in a treatment of PMO [postmenopausal osteoporosis] population, and if the data supported approval, we would consider allowing preliminary language in the labeling regarding once monthly dosing for the prevention of PMO indication. Such language for the prevention of PMO in the Dosage and Administration section might read "alternatively, once monthly dosing may be considered." This approach would require a written commitment from Roche to conduct a Phase 4 study comparing the once-daily to the once-monthly dosing regimen in a prevention of PMO population."

At the pre-NDA meeting for the monthly formulation held on November 25, 2003, the FDA agreed with the applicant's proposal to conduct a placebo-controlled Phase 4 study of monthly ibandronate in the prevention population instead of an active-controlled trial.

On March 24, 2005, FDA approved Boniva 150 mg monthly oral tablet for the treatment of postmenopausal osteoporosis. FDA allowed "preliminary language" on labeling of the 150 mg product related to prevention indication with the understanding that Roche would conduct a Phase 4 study for the prevention indication.

The present submission contains the final study report for the Phase 4 study. In addition, the present submission updates labeling to "physician labeling rule" (PLR) format (21 CFR Parts 201, 314, and 601). The main changes required by the PLR rule are the addition of a summary sections called "Highlights," the addition of a table of contents, and the re-organization of the sections of labeling so that the most frequently consulted sections appear before other sections.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The source of clinical data in the submission was Study BA18492.

### 4.3 Review Strategy

I reviewed the study report for Study BA18492, labeling, and related reviews.

### 4.4 Data Quality and Integrity

I found no evidence of quality or integrity issues with the data.

To decide whether a clinical site should undergo inspection, I looked for disproportional efficacy or adverse event reporting by site. Two sites accounted for more than half of subjects enrolled (Table 1).

**Table 1. Adverse Event Reporting by Site**

Site Number	N of Subjects Enrolled	% of Enrolled Subjects Reporting Any Adverse Event	Relative % Change from Baseline in Mean Lumbar Spine (L2-L4) BMD at 12 Months of Active Treatment (ITT population, unadjusted for time since menopause)
67186	46	100	3.7 (n=21)
67179	39	64	4.8 (n=16)
67189	17	65	2.2 (n=8)
67188	15	80	3.1 (n=7)
67187	11	73	3.7 (n=5)
67191	9	36	3.0 (n=3)
67185	8	100	5.4 (n=3)
67180	6	33	3.0 (n=2)
67348	5	80	0.9 (n=2)
85432	4	75	-2.2 (n=1)
<b>Total</b>	<b>160</b>	<b>78</b>	<b>3.6 (n=68)</b>

Source: Created by reviewer using DEMO, AE, and EFBMDITT datasets and JMP software

Of the two sites that enrolled the most subjects, Site 67179 showed higher than average efficacy and lower than average reporting of adverse events. However, removing the site altogether would not change the efficacy conclusion. Additionally, I contacted FDA's Division of Scientific Investigations to see if Site 67179 had been previously inspected. The site was

inspected in 2004 for an ibandronate study and was found to have minor deficiencies that were corrected.

#### **4.5 Compliance with Good Clinical Practices**

The applicant provided a statement asserting compliance with the U.S. regulations related to informed consent and institutional review boards, as well as with International Conference on Harmonization Good Clinical Practice Guidelines.

#### **4.6 Financial Disclosures**

Investigators and sub-investigators from all ten sites had no financial interests to disclose. The applicant submitted a signed FDA Form 3454 claiming no financial interests or arrangement with the investigators whereby the value of compensation could be affected by the outcome of the study.

### **6 INTEGRATED REVIEW OF EFFICACY**

#### **6.1 Indication**

The proposed indication is prevention of osteoporosis in postmenopausal women.

##### *6.1.1 Methods*

The source of clinical data in the submission was Study BA18492.

##### *6.1.2 General Discussion of Endpoints*

The reason to prevent osteoporosis in postmenopausal women is to reduce the incidence of bone fractures. Fracture reduction is difficult to demonstrate, particularly in women who do not yet have osteoporosis, because of the large numbers of subjects and the long-term follow-up required. FDA accepted increase in BMD as a surrogate endpoint for the proposed indication in Study BA18492.

*Reviewer comments: Acceptance of the BMD endpoint for ibandronate is reasonable because*

- Ibandronate 2.5 mg daily reduces the incidence of new vertebral fractures in a related population, women with vertebral fractures.*
- Data support that the 2.5 mg daily dose and the 150 mg monthly dose have similar effects on bone. A trial comparing the daily 2.5 mg dose to the monthly 150 mg dose in women with osteoporosis showed similar improvements in BMD with both regimens. The mean increase in lumbar spine BMD at 1 year was 3.86% in the 2.5 mg group and 4.85% in the 150 mg group.*

- *Other bisphosphonates have been shown to increase BMD and decrease vertebral fractures in similar populations.*

### 6.1.3 Study Design

Study BA18492 was a double-blind, randomized, controlled, ten-center study conducted in the United States comparing ibandronate to placebo. Group A received ibandronate 150 mg taken orally once monthly and Group B received a matching placebo. All subjects also received 500 mg calcium and 400 IU of vitamin D daily. The primary endpoint, bone mineral density at the lumbar spine, was measured after one year of therapy. Subjects received 12 months of treatment and were followed for an additional 15 days.

Subjects took study drug on the same calendar day each month, in the morning after an overnight fast of six hours or more, in an upright position, and with an 8 oz glass of plain water. After dosing, subjects stayed upright and fasted for at least 60 more minutes. Only water was allowed during the fasting periods. Calcium and Vitamin D were taken in the evening.

Dose selection was based on the results of a previous study, Study BM16549, which was the basis of approval of the 150 mg dose of ibandronate for the treatment of osteoporosis. In that study, the increase in lumbar spine BMD in the 150 mg treatment group was superior to that in the 2.5 mg daily group and the 100 mg monthly treatment group.

Subjects were postmenopausal women with osteopenia.

Main inclusion criteria were

- Ambulatory postmenopausal women 45 to 60 years old
- Mean baseline lumbar spine L2-L4 BMD T-score  $<-1.0$  and  $>-2.5$
- Mean baseline proximal femur BMD T-score  $>-2.5$

The main exclusion criteria were

- Presence of a vertebral fracture at screening, assessed locally by X-ray of T4-L4, or documented low trauma osteoporotic fracture in any other bone
- Severe renal failure (glomerular filtration rate  $<30$  mL/min)
- Malignancy (breast cancer within the last 20 years or any other malignant disease within the last 10 years)
- Disorders influence bone metabolism such as chronic gastrointestinal or liver disease, alcoholism, malabsorption syndrome, hyperparathyroidism, Paget's disease, osteomalacia, untreated thyroid disease
- Other investigational drug within 30 days preceding first dose of study drug
- Treatment with fluoride at a dose greater than 10 mg/d within the last 12 month or for more than two years
- Treatment with parathyroid hormone (PTH) or similar agent within past two years
- Treatment with bisphosphonate during the past two years
- Treatment with other drugs affecting bone metabolism within the last six months such as

- Systemic corticosteroids
- Systemic hormones, anabolic steroids, active vitamin D analogs, calcitonin
- Contraindications for calcium and vitamin D therapy
- Serum total calcium >10.5 mg/dL or < 8.0 mg/dL
- Vitamin D deficiency
- White blood cell count < 2500 per  $\mu$ L
- Alanine aminotransferase (ALT) twice upper limit of normal range
- Serum albumin < 3.0 g/dL
- History of major gastrointestinal (GI) disease defined by:
  - Upper GI bleeding within the last year requiring hospitalization or transfusion
  - Recurrent peptic ulcer disease documented by radiographic or endoscopic means
  - Dyspepsia or gastroesophageal reflux that is uncontrolled by medication
  - Abnormalities of the esophagus that delay esophageal emptying, such as stricture, achalasia, or dysmotility
  - Active gastric or duodenal ulcers

*Comment: Exclusion of subjects with major gastrointestinal disease limits the applicability of the safety findings to a broader population. However, according to a previous medical review of Boniva, the applicant did not exclude women with gastrointestinal disease from the larger Phase 3 studies of Boniva that supported initial approval. (See medical review of NDA 21-455 dated 21-Apr-2003.)*

\* Pre-study visit for each subject took place within 2 months of randomization

Schedule of Assessments						
	Treatment Period					<sup>10</sup> Follow-up
<sup>1</sup> Visit	Screening	1	2	3	4	
month	-2*	0	3	6	12	+15 days
Informed consent	X					
Check inclusion/exclusion criteria	X	X				
Serum 25-hydroxy vitamin D test	X					
Randomization		X				
Demographics	X					
Medical history	X					
Weight and height	X				X	
Physical examination		X				
<sup>2</sup> Safety laboratory	X		X	X	X	
<sup>3</sup> Lateral x-ray of spine T4-L4	X					
BMD proximal femur	X				X	
<sup>4</sup> BMD lumbar spine (L2-L4)	X				X	
<sup>5</sup> sCTX		X	X	X	X	
Concomitant disease and treatment	X	Continuous recording				
<sup>6</sup> Adverse events		Continuous recording				
Study drug dispensed		X		X		
<sup>7</sup> OSCAL <sup>®</sup> supplement dispensed		X		X		
<sup>8</sup> Compliance record (subject)		Monthly				
<sup>9</sup> Compliance phone contact		Performed at month 9 only				

<sup>1</sup> Visits were planned at the appropriate time point in relation to visit 1 (calendar months), and not in relation to the prior visit. Visits had a  $\pm 7$ -day time window.

<sup>2</sup> Safety laboratory: Those laboratory parameters where results indicate a safety concern to the investigator could be retested.

<sup>3</sup> Lateral x-ray of spine T4-L4 was performed at the local lab.

<sup>4</sup> BMD lumbar spine: DXA scan of L2-L4 (mean BMD of at least two vertebrae L2-L4 that were not fractured and not affected by an osteoarthritic process to such a degree that accurate measurement of BMD would be considered jeopardized).

<sup>5</sup> sCTX (serum): The subjects were to be informed that they should stay fasting (following an overnight fast of 6 hours or more) until the blood samples were collected (between 8 and 10 AM).

<sup>6</sup> Adverse Events: Assessment of Adverse Events was performed at each visit, at the follow-up-compliance telephone contact, and at 15 day follow up contact at the end of the study. Clinical fractures that occurred during the study were to be confirmed by an x-ray and a radiologist's report.

<sup>7</sup> OSCAL<sup>®</sup> tablets were to be taken daily in the evening.

<sup>8</sup> Compliance record: Compliance was recorded through subject's marking of study medication blister cards.

<sup>9</sup> Compliance phone contact: Site staff was to call the subjects at month 9 ( $\pm 1$  month) to remind them to take their study medication as instructed and collect any new information regarding adverse events and concomitant treatments.

<sup>10</sup> End of study follow-up: The investigator was to contact the subject 15 days after completion of the 1-year treatment period, or 15 days after the date of discontinuation for subjects who prematurely withdraw from the study, to collect follow-up information about ongoing and new adverse events.

No early termination visit was planned. If discontinuation occurred within 2 months before the last visit, every effort was made to have this visit performed at month 12, including the BMD scan. For all other early terminations, every effort was to be made to obtain complete compliance and safety information to be documented in the case report form.

The primary endpoint was relative percent change from baseline at 12 months in mean BMD of the lumbar spine (mean BMD of at least two vertebrae [L2-L4] that are not fractured, and not affected by an osteoarthritic process or a scanning artifact, to such a degree that accurate

measurement of BMD was jeopardized). A Month 12 BMD was performed at 360 days  $\pm$  69 days from baseline. BMD measurements of lumbar spine L2-L4 with two or more vertebral bodies at L2-L4 identified as fractured, not evaluable, or not fulfilling the quality control of (b) (4) (the central reader) were excluded from the analysis.

BMD was measured by a single dual energy x-ray absorptiometry scan of the lumbar spine and proximal femur at the time of screening and at month 12. BMD was analyzed centrally. The central reading center could request a repeated screening BMD if there were issues about the suitability of the local screening BMD measurement, such as detection of a fracture, an osteoarthritic process, or a scanning artifact, so that accurate measurement of BMD was jeopardized. The central reading center could also request a repeat of the Month 12 BMD scan if the original scan was judged unsuitable.

The primary analysis population was an intent-to-treat (ITT) group. The primary analysis was an analysis of variance including treatment group and time since menopause (as a binary variable; 0.5 to 3 years, and >3 years) as independent factors. The applicant defined the ITT population as all subjects randomized who received at least one dose of the trial medication, and had at least one follow-up data point.

The per protocol (PP) population included subjects who satisfied the ITT criteria and had no major violations of entry criteria or major deviations from the protocol. The safety analysis population included all subjects who had at least one dose of study medication.

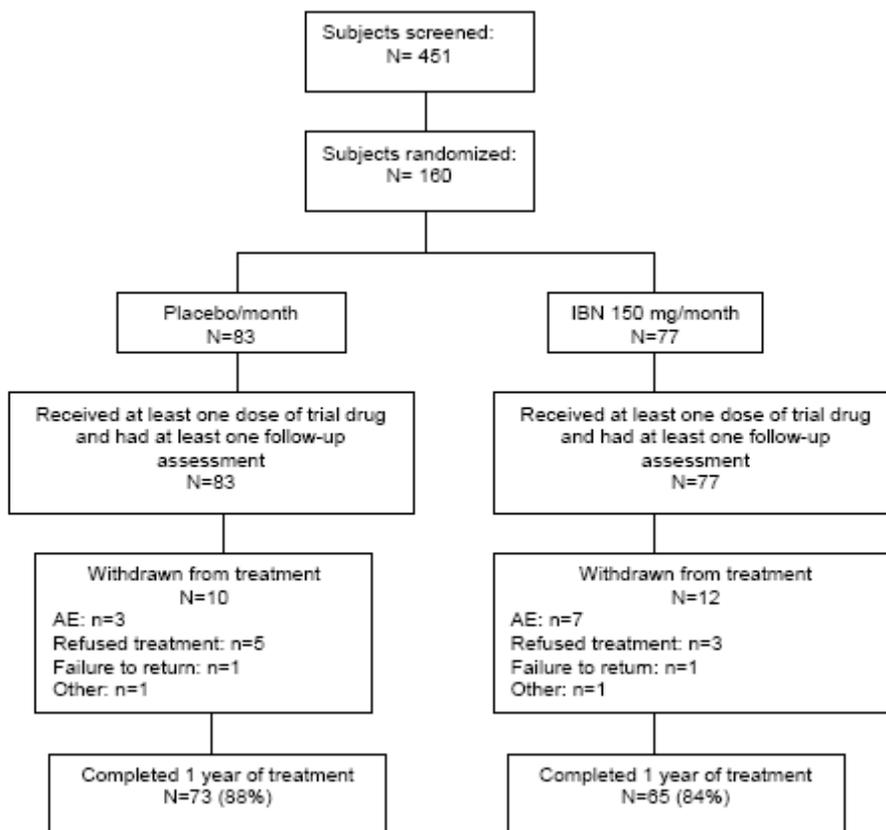
*Comment: Typically, the ITT population is all subjects randomized who received a dose of medication. By requiring a follow-up data point, bias can be introduced if dropouts are different between groups. However, in the study, all subjects randomized had at least one follow-up assessment, and therefore the ITT population conformed to an ITT population as typically defined.*

#### 6.1.4 Efficacy Findings

The study enrolled 160 women with postmenopausal osteopenia; 83 women received placebo and 77 women received ibandronate. The groups were balanced for demographic and baseline characteristics. Twenty-two subjects from the ITT group were not included in the primary efficacy assessment either because they did not have Month 12 lumbar spine BMD data (n=15 [eight from placebo group and seven from ibandronate group]), or because the Month 12 lumbar spine BMD was measured outside a 10-week window of the specified measurement date (n=7, [five from placebo group and two from ibandronate group]).

Figure 1 shows the disposition of subjects.

**Figure 1. Disposition of Subjects**



Most (79%) of the subjects who failed screening did so because they did not meet BMD entry criteria.

Baseline data were comparable between the treatment groups with respect to age, body weight, height, BMI, race, ethnicity, and smoking status. Most subject were “White” (95% in the ibandronate arm, and 96% in the placebo arm). A slightly higher percentage of subjects in the ibandronate arm (23%) than in the placebo arm (18%) reported having a first-degree family member who had low energy osteoporotic fragility fractures. Table 2 shows selected baseline characteristics.

**Table 2. Selected Baseline Characteristics**

<b>Variable</b>	<b>Placebo N=83</b>	<b>Ibandronate N=77</b>
Mean age (years)	53.4	53.7
Mean weight (kg)	70.7	70.2
Mean height (cm)	160.6	160.6
Mean BMI (kg/m <sup>2</sup> )	27.4	27.2
Never smoked (%)	62.7	64.9

Source: From submission file BA18492.pdf, study report for BA18492, Table 6, p. 48

Table 3 shows the primary efficacy analysis and selected supportive analyses.

The study demonstrated efficacy as pre-specified in the protocol. Treatment with 150 mg once monthly ibandronate resulted in a mean *increase* from baseline in lumbar spine BMD of 3.73%, whereas the placebo group had a mean *decrease* of 0.39%.

Of 83 women who took at least one dose of placebo, 70 (84%) were included in the primary efficacy analysis. Of 77 women who took at least one dose of ibandronate, 68 (88%) were included in the primary efficacy analysis.

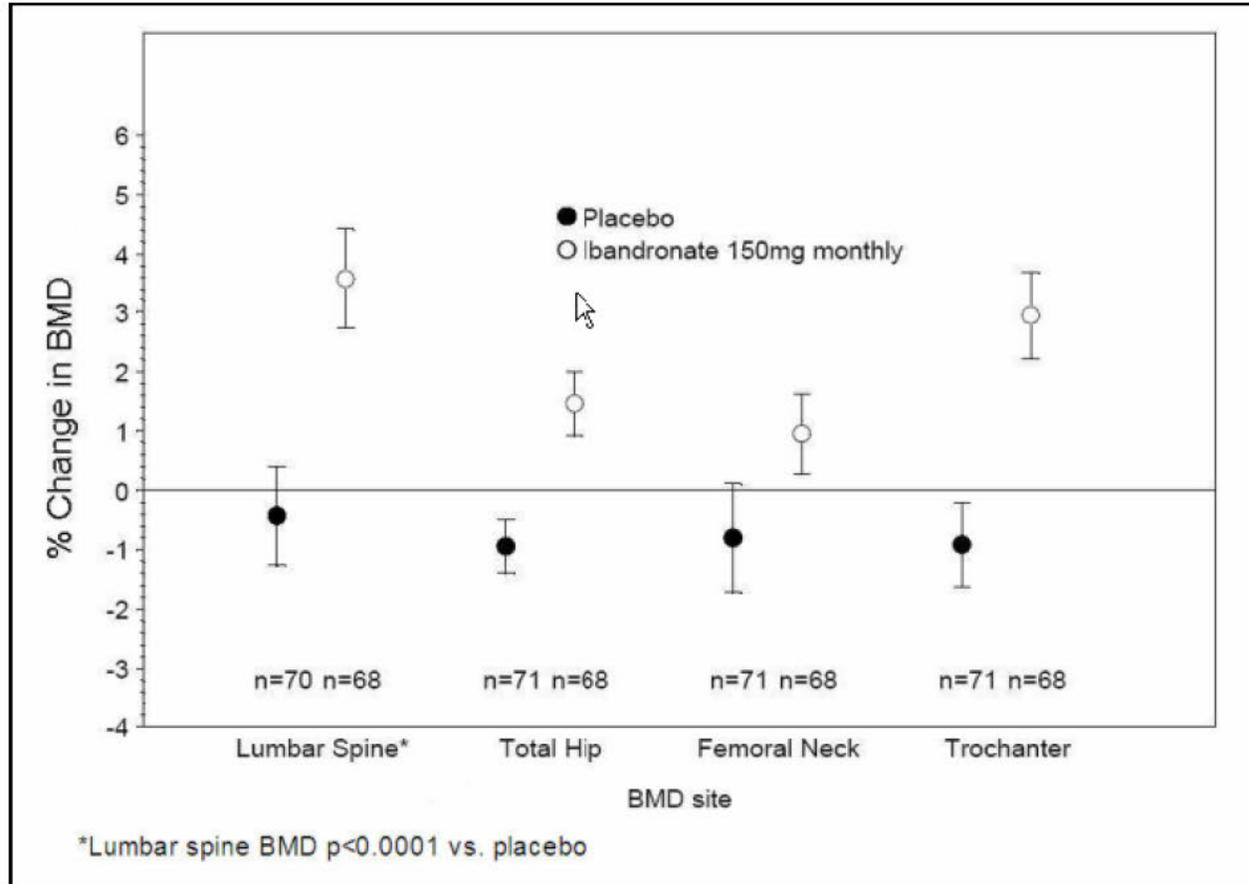
**Table 3. ANOVA of Relative % Change from Baseline at Month 12 of Mean Lumbar Spine BMD**

	Placebo	Ibandronate 150 mg Monthly
<b>Primary Efficacy Analysis</b>		
<i>Intent-to-treat Population*</i>		
n	70	68
Adjusted mean	-0.39	3.73
Treatment effect		4.12
p-value		<0.0001
<b>Secondary Analyses of the Primary Efficacy Parameter</b>		
<i>Per-protocol Population*</i>		
n	60	58
Adjusted mean	-0.28	3.69
Treatment effect		3.98
p-value		<0.0001
<i>Subjects with 0.5 to 3 years since menopause (ITT)</i>		
n	41	42
Adjusted mean	-0.82	3.15
Treatment effect		3.98
p-value		<0.0001
<i>Subjects with &gt; 3 years since menopause (ITT)</i>		
n	29	26
Adjusted mean	-0.08	4.49
Treatment effect		4.58
p-value		<0.0001

\*ANOVA for the comparison of the treatment groups was adjusted for time since menopause (0.5 to 3 years, > 3 years) and baseline BMD (L2-L4) T-score value  
 Source: Submission [overview.pdf], Table 2, p. 13

The applicant provided additional analyses that supported efficacy. For example, Figure 2 shows percent changes in bone mineral density at all sites measured.

**Figure 2. Mean and 95% CI for Relative % Change from Baseline in BMD at Month 12 by BMD Site (ITT Population)**



Source: Submission [overview.pdf], Figure 1, p. 15

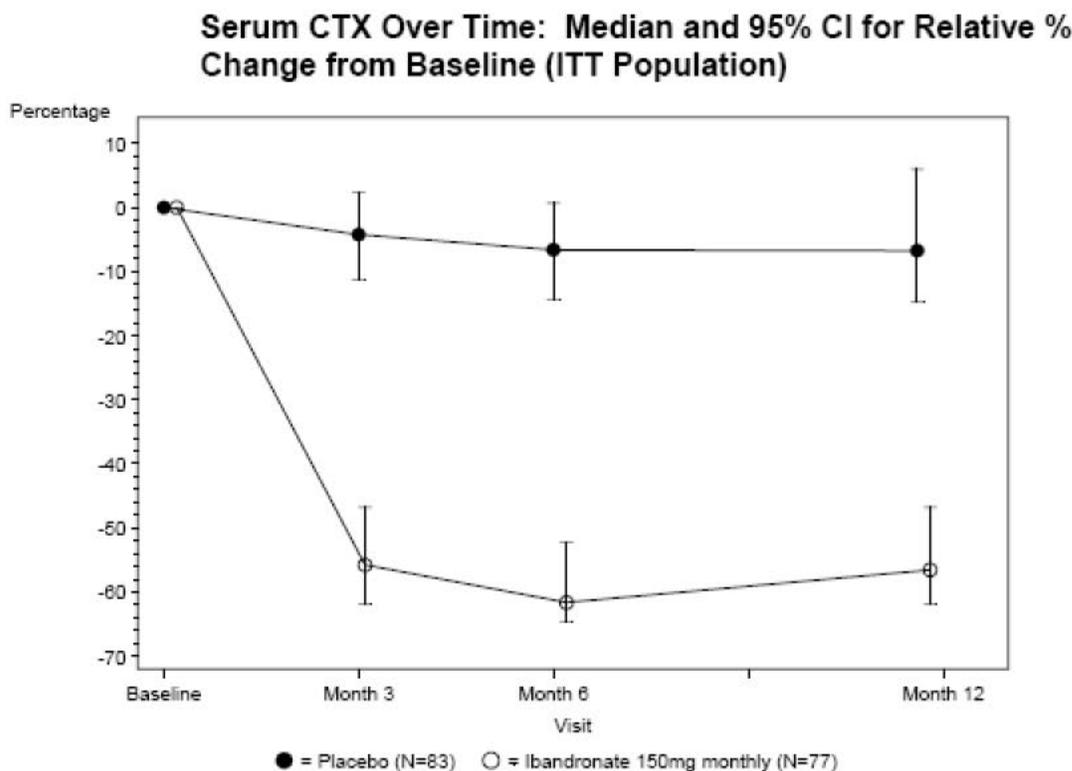
*Comment: On August 11, 2008, Roche submitted corrections to three hip scans after learning that hip scans for 3 of 160 subjects were affected by a defect in an upgraded version of analyzing software. The corrections changed the point estimates in Figure 2 minimally, as follows:*

- *BMD increase relative to baseline for total hip, changed from 1.46% to 1.49%*
- *BMD increase relative to baseline for femoral neck, changed from 0.95% to 1.09%*
- *BMD increase relative to baseline for trochanter, changed from 2.94% to 2.87%*

Serum levels of the C-telopeptide of the alpha chain of type I collagen (CTX) were measured at baseline and at Months 3, 6, and 12. A decrease in serum CTX indicates a decrease in bone resorption. Subjects treated with ibandronate had a median decrease of CTX of 56% at Month 3, which was sustained through Month 12. Subjects treated with placebo had little change in serum CTX levels (Figure 3).

*Comment: The relevance of decreased bone remodeling to a desirable clinical outcome is unclear.*

**Figure 3. Serum CTX over Time: Median and 95% CI for Relative % Change from Baseline (ITT Population)**



Source: Submission file labeled [overview.pdf], p. 16

Two of my own exploratory analyses did not provide additional support for efficacy

- Mean change in height from baseline to Month 12. Height changes did not support efficacy of ibandronate in the current submission (Table 10) because the ibandronate group had a small loss in mean (-0.6 cm) and median height (-1.0cm), whereas the placebo group had a small increase in mean height (0.7 cm) and no change in median height (0.0 cm). However, the 95% confidence intervals around the estimates of height change overlapped. The increase in mean height in the placebo group suggests that measurements were not well-standardized. (In the larger pivotal trial supporting initial approval of 2.5 mg ibandronate daily, there was a -0.04 cm yearly difference in mean height between placebo group and 2.5 mg ibandronate group, favoring ibandronate.)
- Number of bone fractures in each group. Two subjects in each group had non-vertebral fractures on treatment. No vertebral fractures were reported.

*Comment: The findings related to non-vertebral fracture in the current submission are consistent with previous studies. Ibandronate did not reduce the risk of non-vertebral fractures in the three-year pivotal trial that supported approval of 2.5 mg daily for treatment of osteoporosis. In the three-year trial for treatment, 9% of subjects in the ibandronate 2.5 mg group (n=977)*

*sustained non-vertebral fractures, whereas 8% of subjects in the placebo group (N=975) sustained non-vertebral fractures. In contrast, the rate of vertebral fracture (clinical plus radiological) was 9.6% for the placebo group and 4.7% for the ibandronate group. The data supporting no effect of BONIVA on non-vertebral fractures are as robust as the data supporting a salutary effect of BONIVA on vertebral fractures.*

#### 6.1.6 Efficacy Conclusions

Study BA18492 supported the efficacy of ibandronate in prevention of osteoporosis in postmenopausal women by meeting the pre-specified efficacy endpoint. The mean percentage change from baseline in lumbar BMD density after one year of treatment was 3.73% for 68 subjects treated with ibandronate, compared with -0.39% for 70 subjects treated with placebo. The p-value for the comparison was less than 0.0001. The applicant also provided analyses of responders, subgroup, per protocol groups, and BMD at non-vertebral sites, all of which were supportive. Small changes in mean and median height did not support efficacy; however, the 95% confidence intervals around the height changes between treatment groups overlapped considerably.

By itself, Study BA18492 would be insufficient to support approval for prevention of osteoporosis. Bone mineral density is a surrogate endpoint that does not always link to the bone fractures, the relevant clinical event. However, previous studies of ibandronate provided support for prevention of vertebral fracture in postmenopausal women using ibandronate. A three-year placebo-controlled study of 2,946 postmenopausal women with a history of vertebral fractures showed that a daily dose of 2.5 mg ibandronate reduced the risk of vertebral fractures by approximately 50%. Furthermore, a one-year study linked the 2.5 mg daily dose to the 150 mg monthly dose of ibandronate by showing that the 150 mg monthly dose of ibandronate was non-inferior to the 2.5 mg daily dose in percent change from baseline in lumbar spine BMD. The study involved 1,602 postmenopausal women with osteoporosis. Taken together, the results of all three studies provide reasonable support for the efficacy of ibandronate in preventing osteoporosis in postmenopausal women.

Study BA18492 was consistent with previous studies of ibandronate: ibandronate did *not* prevent non-vertebral fractures. Two subjects in the placebo group and two subjects in the ibandronate group had non-vertebral fractures during treatment.

No vertebral fractures occurred in either treatment group. However, the study was not designed to show a difference in vertebral fracture risk: the small number of subjects, the short duration of the study, and the population (osteopenic, not osteoporotic women) made it unlikely that many vertebral fractures would occur.



### 7.1.2 Other Serious Adverse Events

There were four serious adverse events (SAEs) reported in Study BA18492 (three in the active treatment arm and one in the placebo arm).

The SAEs in the active treatment arm were

- Acute pyelonephritis starting on Day 105 in a subject with bladder prolapse (Subject 1015)
- Non-cardiac chest pain, diagnosed as gastroesophageal reflux disease on Day 5, discontinued study. (Subject 1380, see narrative in the next section)
- Upper limb fracture and dislocation following a fall from a ladder on Day 163, discontinued study. (Subject 1367, see narrative for this subject in the next section.)

The SAE in the placebo arm was

- Cellulitis (Day 38) following trauma to the hand (Subject 1376)

### 7.1.3 Dropouts and Other Significant Adverse Events

More subjects in the active treatment group than the placebo group discontinued for adverse events (seven compared with three). In the treatment group, three subjects complained of symptoms consistent with muscle pain (“myalgia,” “severe muscle pain,” “cramps”) shortly following treatment; the two subjects with “myalgia” or “severe muscle pain” demonstrated a challenge-rechallenge pattern. (See Table 4 and Table 5 for more details of the challenge-rechallenge pattern.)

In the active treatment arms, discontinuations included:

1. Subject 1370, a 48-year-old woman had flu-like symptoms including headache, **myalgia**, and arthralgia, following each of seven monthly doses of ibandronate. She also experienced heartburn and an episode of pyelonephritis.
2. Subject 1192, a 55-year-old woman experienced **severe muscle pain** following each of four monthly doses of ibandronate (Day 2, Day 32, Day 65, and Day 93).
3. Subject 1012, a 50-year-old woman had gastroesophageal reflux disease starting on Day 156.
4. Subject 1249, a 54-year-old woman, had weight increase starting on Day 3. She reported four pounds of weight gain in Month 3.
5. Subject 1367, a 51-year old woman had an upper limb fracture starting on Day 161 following a fall from a ladder.

6. Subject 1380, a 52-year-old woman had chest pain starting on Day 5. She was hospitalized overnight and discharged with the diagnosis “GERD” (gastroesophageal reflux disease).
7. Subject 1503, a 48-year-old woman received her first dose of ibandronate on 13-Jul-06, and, on 15-Jul-06 complained of nausea, upset stomach, *cramps*, and fatigue. She discontinued therapy and the investigator listed her outcome (date not noted) as “unresolved.”

In the placebo treatment arm, discontinuations included:

1. Subject 1129, a 57-year-old woman taking placebo, had peri-arthritis that was present at baseline and was reported again after four monthly injections.
2. Subject 1364, a 51-year-old woman taking placebo, had gastroesophageal reflux disease. Symptoms of vomiting occurred about two weeks after her Month 8 dose. She also had toe fracture when she walked into a bed frame at night.
3. Subject 1188, a 52-year-old woman taking placebo, had heartburn about two weeks after taking her first dose of placebo.

**Table 4. Time Course of “Flu like symptoms” for Patient 1370 to Show Challenge-Rechallenge**

<b>Treatment Date</b>	<b>AE start date</b>	<b>Duration of AE (days)</b>	<b>Description of AE (investigator text)</b>
17Apr06	17April06	4	Flu like symptoms: headache, <i>myalgia</i> , arthralgia
18May06	18May06	5	Flu like symptoms following study medication
18May06	23May06	3	<i>Myalgia</i> worsening
18Jun06	18Jun06	5	Flu like symptoms following study medication
16Jul06	16Jul06	7	Flu like symptoms following study medication
16Aug06	16Aug06	7	Flu like symptoms following study medication
19Sep06	19Sep06	7	Flu like symptoms following study medication
16Oct06	16Oct06	7	Flu like symptoms following study medication
17Oct06	17Nov06	7	Flu like symptoms following study medication

Source: Created by reviewer from datasets “MEDT” and “AE”

**Table 5. Time Course of Muscle Pain or Weakness for Patient 1192 to Show Challenge-Rechallenge**

<b>Treatment Date</b>	<b>AE start date</b>	<b>Duration of AE (days)</b>	<b>Description of AE (investigator text)</b>
08Apr06	09Apr06	5	<i>Muscle pains</i> , arms and legs bilaterally, <i>Muscle weakness</i> -arms and legs bilaterally
08May06	09May06	8	<i>Muscle pain</i> , complaints of <i>severe muscle</i> /joint pains-generalized, subject states pain was the worst while sitting or standing, pain lessened while lying down.
08Jun06	11Jun06	4	<i>Muscle weakness</i>
08Jul06	09Jul06	4	<i>Severe muscle pain-back region</i>

Source: Created by reviewer from datasets “MEDT” and “AE”

*Comment: Current labeling regarding musculoskeletal pain notes that these symptoms have been reported “postmarketing,” and such reports are “infrequent.” However, in this study of 77 subjects treated with ibandronate, two subjects had musculoskeletal complaints that were severe*

*enough for them to drop out of the study, and they had a strong challenge-rechallenge pattern. A third subject had “cramps” and other symptoms resulting in dropout from the study.*

*The pattern seen with challenge-rechallenge was onset within one to three days of dosing, followed by persistence for four to eight days. A plausible reason for the muscle complaints is hypocalcemia because myalgia is a symptom of hypocalcemia, and because the time course for myalgia is similar to the expected time course reported in the literature for effects of ibandronate on calcium. In Study BA18492, serum calcium levels were not obtained during the week following administration of ibandronate, and therefore the myalgia events cannot be correlated with hypocalcemia. However, in a published study<sup>1</sup>, 10 of 15 subjects who received 3 mg intravenous ibandronate developed hypocalcemia that lasted for a median of 7 days, with the lowest serum calcium occurring on Day 3.*

*No one in the placebo group discontinued with similar complaints. This section of labeling should be strengthened.*

One subject, 67179/1244, was initially reported with the serious adverse event “helicobacter infection,” but the investigator requested that the event be reclassified as an adverse event (AE). The subject took ibandronate. The event occurred on Day 75 through Day 85. The subject was treated with Prevpac, a combination product indicated for the treatment of Helicobacter pylori infection and duodenal ulcer disease.

*Comment: Subject 1244 should be counted as having had a gastrointestinal ulcer unless the applicant provides information to refute the diagnosis. The verbatim term for the re-classified AE was H pylori, a cause of gastrointestinal ulcers. The diagnosis H pylori, and the choice of medication, are presumptive evidence of ulcer disease. I requested more information, including an evaluation of source records if necessary, to confirm the diagnosis of ulcer. The applicant did not evaluate source records, but instead queried the investigator who was not the treating physician for “H pylori.” The investigator then contacted the subject and asked if she could recall any “significant symptoms which might suggest ulcer disease.” She did not recall such symptoms. However, the interval of time from her diagnosis to the investigator’s contact in response to our request was about two years. It seems unlikely that recall would be reliable over two years. The diagnosis H pylori and the choice of medication remain presumptive evidence of ulcer disease. According to labeling, ulcers have been reported as postmarketing events for ibandronate, but not as premarketing events. This is a premarketing report.*

#### 7.1.4 Other Search Strategies

Radiologically-confirmed clinical fractures that occurred during the trial were reported as adverse events. Two subjects in the placebo arm and two subjects in the active arm had clinical fractures. All fractures were associated with trauma.

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<sup>1</sup> Pecherstorfer M, Ludwig H, Schlosser K, et al. Administration of the bisphosphonate ibandronate by intravenous bolus injection. J Bone and Min Res 11:587, 1966

**Table 6. Fractures by Subject in Study BA18492**

<b>Subject</b>	<b>Treatment</b>	<b>Type of Fracture</b>	<b>Treatment Day of Onset</b>
1364	Placebo	Intra-articular fracture, right foot	14
1533	Placebo	Left foot fracture	133
1130	Ibandronate	Colles fracture, left wrist	144
1367	Ibandronate	Rib fractures, bilateral, and fracture of radial head with elbow dislocation	161

Source: p. 422, Clinical Study Report BA18492

*Comment: This study did not provide evidence for one clinically relevant outcome, prevention of non-vertebral fractures. Although the study was not designed to test for prevention of fractures, the fracture results are consistent with the results of a previous larger study in which ibandronate therapy failed to prevent non-vertebral fractures (Study 4411, reviewed in medical review dated 21-Apr-2003).*

#### 7.1.5 Common Adverse Events

The background noise for health complaints in the studied population made it difficult to detect adverse events related to drug use by looking at the applicant's tables of common adverse events (Table 7). Gastrointestinal and muscular complaints emerged as treatment-related effects when I explored the data for events that occurred within a few days of drug intake. (See Section 7.1.3.)

Overall, the frequency of reports of adverse events was similar between treatment groups, with 77.9% of subjects taking ibandronate and 77.1% of subjects taking placebo reporting any adverse event. Arthralgia and myalgia occurred more often in the ibandronate group, which is consistent with labeling (Table 8). The difference between treatment groups with respect to gastrointestinal and muscular complaints becomes more apparent when the adverse event database is explored for complaints that occur within the first five days of dosing (see Section 7.4.2.2).

**Table 7. Summary of On-Treatment Adverse Events by Body System (Safety Population)**

<b>MedDRA Body System/Adverse Event</b>	<b>Ibandronate N=77 n (%)</b>	<b>Placebo N=83 n (%)</b>
Total Adverse Events	60 ( 77.9)	64 ( 77.1)
Musculoskeletal and connective tissue disorders	26 ( 33.8)	27 ( 32.5)
Gastrointestinal disorders	24 (31.2)	20 ( 24.1)
Infections and infestations	20 ( 26.0)	32 ( 38.6)
General disorders and administration site conditions	9 ( 11.7)	3 ( 3.6)
Injury, poisoning and procedural	8 ( 10.4)	7 ( 8.4)
Nervous system disorders	8 ( 10.4)	7 ( 8.4)
Psychiatric disorders	8 ( 10.4)	4 ( 4.8)
Metabolism and nutrition disorders	8 ( 10.4)	3 ( 3.6)
Skin and subcutaneous tissue disorders	7 ( 9.1)	10 (12.0)
Respiratory, thoracic and mediastinal disorders	6 ( 7.8)	2 ( 2.4)
Investigations	3 ( 3.9)	4 ( 4.8)
Reproductive system and breast disorders	3 ( 3.9)	4 ( 4.8)
Vascular disorders	3 ( 3.9)	3 ( 3.6)
Ear and labyrinth disorders	2 ( 2.6)	2 ( 2.4)
Eye disorders	2 ( 2.6)	1 ( 1.2)
Endocrine disorders	-	3 (3.6)
Immune system disorders	1 ( 1.3)	2 ( 2.4)
Renal and urinary disorders	1 ( 1.3)	2 ( 2.4)
Blood and lymphatic system disorders	2 ( 2.6)	-
Cardiac disorders	1 ( 1.3)	1 ( 1.2)
Congenital, familial and genetic disorders	1 ( 1.3)	-
Neoplasms benign, malignant and unspecified (incl cysts)	1 ( 1.3)	-

Source: study report for Protocol BA 18492, Table 41, page 81

**Table 8. Adverse Events Reported in > 5% of Subjects in Either Treatment Group by MedDRA Preferred Term (Safety Population)**

Preferred Term	Ibandronate 150 mg monthly N=77	Placebo N=83
Arthralgia	12 (15.6)	8 (9.6)
Myalgia	5 (6.5)	2 (2.4)
Upper respiratory tract infection	5 (6.5)	12 (14.5)
Nausea	5 (6.5)	3 (3.6)
Pain in extremity	5 (6.5)	5 (6.0)
Dyspepsia	4 (5.2)	4 (4.8)
Dental caries	4 (5.2)	3 (3.6)
Gastroesophageal reflux disease	4 (5.2)	3 (3.6)
Headache	4 (5.2)	4 (4.8)
Insomnia	4 (5.2)	1 (1.2)
Hypercholesterolemia	4 (5.2)	1 (1.2)
Back pain	2 (2.6)	5 (6.0)

Source: Submission Item 8, Table 7, page 20

*Comments: The significance, if any, of the hypercholesterolemia among subjects treated with ibandronate is unclear. Hypercholesterolemia is not a reported complication of ibandronate therapy, although in this study investigators reported more cases of hypercholesterolemia among the subjects in the ibandronate group. I explored the laboratory data set and found that only one of the five subjects had cholesterol level above the upper limits of normal at any of the routine laboratory evaluations. (Subject 1181 had one cholesterol level of 108 mmol/L.) The upper limit of normal for the laboratory was 106 mmol/L. The remaining four subjects had cholesterol levels that remained in the normal range and showed very little change from baseline. However, four subjects were started on statin therapy during the study, suggesting that the cholesterol elevation was diagnosed with a laboratory test that was not done as part of the study.*

#### 7.1.7 Laboratory Findings

Safety laboratory tests, done at screening and months 3, 6, and 12, included:

- Hematology
- Chemistry (albumin, creatinine, blood urea nitrogen, alanine aminotransferase (ALT), total calcium, phosphate, magnesium, sodium, potassium, and chloride)

Serum 25-hydroxy vitamin D was tested at screening to determine eligibility. Blood for laboratory tests was taken immediately before subjects received their monthly study medication, and therefore at the likely nadir of monthly serum levels of ibandronate.

*Comment: The timing of laboratory tests, at the concentration nadir for ibandronate, made it unlikely that any acute, drug-related electrolyte changes would be detected. In a published*

study<sup>2</sup>, 10 of 15 subjects who received 3 mg intravenous ibandronate developed clinically asymptomatic hypocalcemia that lasted for a median of 7 days, with the lowest serum calcium occurring on Day 3. It is interesting that this time course for hypocalcemia is similar to the time course for myalgia that was observed for two of the subjects who dropped out of Study BA18492. Additionally, FDA has received postmarketing reports of hypocalcemia following oral dosing of ibandronate.<sup>3</sup>

There were no clinically relevant changes in mean laboratory values, and no dropouts for abnormal laboratory values. There were no ALTs greater than three times the upper limit of normal. Mean change from baseline appeared similar in both treatment groups at all time points. To illustrate, Table 9 shows mean change from baseline for serum calcium by visit. Two subjects had calcium levels below the normal minimum for the laboratory (8.6mg/dL), one in the placebo group (8.4 mg/dL) and one in the ibandronate group (8.3 mg/dL).

Four subjects met the applicant's criteria for marked laboratory abnormalities, all in the placebo arm (single low white blood cell count, a single high phosphate, and two subjects had single value of ALT approximately 2.5 times the upper limit of normal).

**Table 9. Mean Change from Baseline in Serum Calcium (mmol/L) by Visit**

	<b>Ibandronate (n)</b>	<b>Placebo (n)</b>
Baseline N	77	83
Month 3	-0.01 (71)	-0.01 (79)
Month 6	-0.04 (70)	-0.01 (77)
Month 12	-0.04 (72)	-0.05 (77)
Last Day	-0.04 (77)	-0.05 (81)

Source: study report for Study BA18492, p. 244

### 7.1.8 Vital Signs

Only weight and height were assessed on treatment. Although the study report did not provide an analysis of weight and height data, the datasets made it possible for me to assess mean and median changes in height and weight by treatment group.

Height changes did not provide support efficacy of ibandronate (Table 10) because the ibandronate group had a small loss in mean and median height, whereas the placebo group had a small increase in mean height and no change in median height. However, the 95% confidence intervals around the estimates of height change overlapped.

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2 Pecherstorfer M, Ludwig H, Schlosser K, et al. Administration of the bisphosphonate ibandronate by intravenous bolus injection. *J Bone and Min Res* 11:587, 1966

3 Search done on 24-Jun-08 of FDA's Adverse Event Reporting System, using the terms "ibandronate," "blood calcium decreased," and "oral" revealed 9 cases. Sample history: 49 year old woman had a normal serum calcium two days before taking ibandronate 150 mg. Five days after taking ibandronate 150 mg, she complained of tingling all over. She had a low serum calcium level (5.7 mg/dl) for which she was admitted to the hospital. She was treated for three days in the hospital before her calcium levels resolved.

Weight changes were similar between treatment groups (Table 11).

**Table 10. Change in Height from Baseline to Final Visit by Treatment Group**

	Ibandronate N=72	Placebo N=77
Mean height change in cm	-0.6	0.7
95% CI of mean height change	-3.0 to 1.7	-1.2 to 2.5
Median height change in cm	-1.0	0.0

Source: Calculated by reviewer from datasets “EFEX2A” and “MEDT”

**Table 11. Change in Weight from Baseline to Final Visit by Treatment Group**

	<b>Ibandronate</b> <b>N=73</b>	<b>Placebo</b> <b>N=77</b>
Mean weight change in kg	0.2	0.3
95% CI of mean weight change	-0.7 to 1.2	-0.3 to 0.9
Median weight change in kg	0.5	0.0

Source: Calculated by reviewer from datasets “EFEX2A” and “MEDT”

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure is summarized in Table 12.

**Table 12. Summary of Duration of Study Treatment (ITT Population)**

	<b>Placebo</b> <b>N=83</b>	<b>Ibandronate</b> <b>N=77</b>
Mean duration in months	11.2	11.0
Median duration in months	12.0	12.0

Source: Table 38, Study Report BA18492

### 7.2.2.2 Postmarketing experience

FDA safety evaluators are currently analyzing postmarketing data for all bisphosphonates for atrial fibrillation to see if there is a class effect that warrants a labeling change. The analysis is ongoing.

### 7.2.2.3 Literature

A search of PubMed for “ibandronate” revealed numerous articles describing an off-label use to treat hypercalcemia secondary to metastatic cancer.

### 7.2.3 Adequacy of Overall Clinical Experience

The applicant provided an adequate clinical database to achieve the objective of the study, to provide support for prevention of osteoporosis.

### 7.2.5 Adequacy of Routine Clinical Testing

Testing was adequate for the objective of the study.

### 7.2.8 Assessment of Quality and Completeness of Data

The data were adequate for the objective of the study. The initially supplied datasets were suboptimal for electronic review, but the applicant responded promptly to reviewer’s requests for adequate datasets.

### 7.2.9 Additional Submissions, Including Safety Update

The four-month safety update correspondence consisted of the following statements:

“No other clinical studies have been conducted nor are being conducted with monthly ibandronate for the prevention of bone loss in postmenopausal osteopenic (non-osteoporotic) women. Therefore, no new safety information has been learned about the use of the 150 mg dose of Boniva (in that setting) that impacts the draft labeling submitted with the prevention sNDA. Base on this, Roche is not submitting a 4-month safety update for the subject application.”

## **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

No new safety signals emerged in Study BA18492. However, the safety findings support upgraded labeling with respect to musculoskeletal pain and gastrointestinal effects. Current labeling indicates that these events have only been detected as postmarketing reports. However, the data from Study BA18492 support musculoskeletal pain and gastrointestinal complaints as AEs that have occurred premarketing, and that occur frequently enough to be apparent in a small clinical trial. The time dependency analyses in the following section provide further support for strengthening labeling with respect to gastrointestinal and muscle effects (Section 7.4.2.2).

## 7.4 General Methodology

### 7.4.2 Explorations for Predictive Factors

#### 7.4.2.2 Explorations for time dependency for adverse findings

The high level of background noise for gastrointestinal and musculoskeletal complaints prevented detection of safety signals when common adverse events occurring over a one year period are compared between placebo and treatment groups.

To enrich the adverse events for conditions likely to be related to acute exposure to drug, I looked at reports of adverse events that occurred within five days of dosing. I chose the first five days post-dose because it seemed likely that drug-related adverse events would occur when drug levels were highest. Five days post-dose roughly corresponds to the terminal half-life of ibandronate 150 mg, and five days post-dose also covers the time when calcium levels decline most based on a published study of an intravenous formulation.

Twenty-one subjects reported 31 adverse events occurring within five days of the first dose of study medication. Twenty-four of 31 adverse events occurred in the ibandronate group. Despite the small number of events reported, Table 13 shows a profile of a drug associated with muscular aches and gastrointestinal disturbances.

**Table 13. Adverse Events Reported within the First Five Days of the First Dose of Therapy, by Treatment Group**

Adverse Event Preferred Term	Ibandronate N=77	Placebo N=83
<b>Total</b>	<b>24</b>	<b>7</b>
Nausea	3	1
Influenza like illness*	3	-
Dyspepsia	2	-
Weight increased	1	1
Gastroenteritis	1	
Stomach discomfort	1	-
Myalgia	1	1
Muscular weakness	1	-
Muscle spasms	1	-
Hypoesthesia**	1	-
Gastroesophageal reflux disease	1	1
Fatigue	1	-
Faecal incontinence	1	-
Diarrhoea	1	-
Depression	1	-
Chest pain	1	-
Back pain	1	-
Arthralgia	1	-
Abdominal pain, lower	1	-
Headache	-	2
Joint crepitation	-	1

\*Investigator text for each of the three AEs coded influenza like illness:

- “nausea, myalgia, lethargie (sic), patient took no medications, spent 2 days in bed”
- “Flu like symptoms: headache, myalgia, arthralgia, Tylenol used”
- “Myalgia, arthralgia, fever occurred post first study medication”

\*\*Investigator text: “numbness of fingers of left hand”

Source: Created by reviewer from DEMO and AE datasets using JMP software

Table 14 shows a slightly different presentation of adverse event data for all adverse events reported between Days 30 and 35, just after the second dose of study medication. The first four subjects, all of whom received ibandronate, have a similar “moderate” reaction of diffuse muscle pain, lasting several days, and starting within one or two days of treatment. However, myalgia and muscle spasms (n=2) are also noted in the placebo group. Looking further than the MedDRA preferred terms, however, shows that the complaints in the placebo group are localized to particular muscle groups, as might be expected if caused by, for example, muscle strain.

**Table 14. Adverse Events reported between Days 30 and 35\***

<b>Adverse Event Preferred Term</b>	<b>Ibandronate</b>	<b>Placebo</b>	<b>Investigator text, comments, and severity ratings</b>
Influenza like illness	3	0	Case 1: Started Day 31, lasted 2 days, “chills, myalgia after taking the study tablet, went to bed with many blankets, resolved in am,” moderate Case 2: Started Day 32, lasted 3 days, “myalgia, arthralgia, fatigue, diarrhea after second dose of medication,” moderate Case 3: started Day 32, lasted 5 days, moderate
Myalgia	1	0	“Muscle pain,” lasted 8 days, started Day 32, “complaints of severe muscle/joints pains –generalized. Subjects states pain was the worst while sitting or standing,” severe
Arthralgia	0	1	“Right knee pain” lasted 173 days, moderate, (“right knee swollen, intermittent”) “Left knee pain,” lasted six days, mild (started Day 34)
Nausea	0	1	Mild, lasted 1 day, started Day 30
Myalgia	0	1	Back myalgia, mild, lasted 1 day, started Day 30
Muscle spasms	0	1	“Low back spasms,” moderate, lasted 5 days, started Day 33
Postmenopausal hemorrhage	1	0	Mild, lasted 5 days, started Day 31
Tooth injury	1	0	“Broken tooth”
Total	6	4	

\*Actual treatment date for second dose of study medication ranged from Day 29 to Day 32 for the subjects in the table

Source: Created by reviewer from DEMO, AE, and MEDT datasets using JMP software

*Comment: Some of the adverse events (e.g. muscle pain, muscle weakness, hypesthesia) are consistent with symptoms of hypocalcemia.*

Reports of adverse events were more frequent for the ibandronate group shortly after dosing, and were similar between groups shortly before dosing. Table 15 shows a summary of adverse events reported within five days following any dose of study drug. Adverse events, particularly musculoskeletal and gastrointestinal complaints, occur more frequently in the subjects treated with ibandronate. The seventeen reports coded as “influenza like illness” came from four subjects who provided 13 instances of challenge-rechallenge. Investigator comments for two of them reported that the patients were bedridden (“went to bed,” “spent 2 days in bed”), suggesting significant effect. One of the subjects with “influenza like illness” discontinued therapy.

**Table 15. Adverse Events (Preferred Terms) Reported within Five Days after Any Dose of Study Drug**

<b>Preferred Term</b>	<b># Reports Ibandronate N=77</b>	<b># Reports Placebo N=83</b>
<b>Total Reports</b>	<b>86 (from 33 subjects)</b>	<b>24 (from 17 subjects)</b>
Influenza like illness	17	-
Arthralgia	6	3
Myalgia	5	2
Nausea	5	3
Dyspepsia	4	-
Gastroesophageal Reflux Disease	4	1
Abdominal Pain Upper	2	1
Depression	2	-
Fatigue	2	1
Headache	2	2
Muscle Spasms	2	1
Muscular Weakness	2	-
Abdominal Pain Lower	1	-
Alopecia	1	-
Angina Pectoris	1	-
Back Pain	1	1
Chest Pain	1	-
Constipation	1	-
Dehydration	1	-
Dental Caries	1	-
Diarrhoea	1	-
Faecal Incontinence	1	-
Flatulence	1	-
Fungal Skin Infection	1	-
Gastroenteritis	1	-
Hypercalcaemia	1	-
Hypercholesterolaemia	1	-
Hypertension	1	-
Hypoaesthesia	1	-
Influenza	1	-
Lymphadenopathy	1	-

<b>Preferred Term</b>	<b># Reports Ibandronate N=77</b>	<b># Reports Placebo N=83</b>
Musculoskeletal Pain	1	-
Neck Pain	1	-
Osteoarthritis	1	-
Postmenopausal Haemorrhage	1	-
Postnasal Drip	1	-
Pyrexia	1	-
Sinusitis	1	1
Stomach Discomfort	1	-
Tooth Injury	1	-
Urinary Tract Infection	1	-
Urticaria	1	-
Vertigo	1	-
Vomiting	1	-
Weight Increased	1	1
Dry Skin	-	1
Flight Of Ideas	-	1
Insomnia	-	1
Joint Crepitation	-	1
Menopausal Symptoms	-	1
Oral Herpes	-	1
Pain In Extremity	-	1

Source: Created by reviewer by joining datasets MEDT and AE and selecting summarizing rows where the AE started within five days following dosing

In contrast, Table 16 shows that the number of adverse events is similar in both groups one to five days before each dose.

**Table 16. Adverse Events (Preferred Terms) Reported within Five Days before Any Dose of Study Drug**

<b>Preferred Term</b>	<b># Reports Ibandronate N=77</b>	<b>#Reports Placebo N=83</b>
<b>Total number of reports</b>	<b>21</b>	<b>27</b>
Arthralgia	3	1
Insomnia	2	-
Pain In Extremity	2	1
Abdominal Pain Lower	1	-
Congenital Cystic Kidney Disease	1	-
Diabetes Mellitus Non-Insulin-Dependent	1	-
Fatigue	1	1
Gastroenteritis Viral	1	-
Gout	1	-
Hot Flush	1	-
Hypercholesterolaemia	1	1
Infection	1	-
Myalgia	1	1
Pharyngolaryngeal Pain	1	-
Rash	1	-
Sinusitis	1	1
Weight Increased	1	-
Back Injury	-	1
Back Pain	-	3
Bronchitis	-	1
Constipation	-	1
Depression	-	1
Ear Infection	-	1
Exostosis	-	1
Eye Injury	-	1
Hypertriglyceridaemia	-	1
Joint Sprain	-	1
Muscle Spasms	-	1
Nasopharyngitis	-	1
Neck Pain	-	1
Sciatica	-	1
Toothache	-	1
Upper Respiratory Tract Infection	-	4

Source: Created by reviewer by joining datasets MEDT and AE and selecting summarizing rows where the AE started one to five days before any dose of study medication

#### 7.4.2.3 Explorations for drug-demographic interactions

There were too few subjects of different races to do a meaningful analysis: one “Asian” in each treatment group; one “Black” in the ibandronate group, none in the placebo group; and two “Others” in each treatment group.

#### 7.4.2.4 Explorations for drug-disease interactions

Women with hypertension might be more vulnerable to electrolyte disorders because of concomitant therapy. Therefore, I explored the AE dataset for AEs among the 32 women with a diagnosis of hypertension. Twenty-two (9 subjects received placebo, 13 subjects receiving ibandronate) of 32 subjects with hypertension had 79 adverse events. I did not find a preponderance of any particular adverse event by preferred term in the ibandronate group.

#### 7.4.2.5 Explorations for drug-drug interactions

I did not explore the data in Study BA18492 for drug-drug interactions because the study was small and no interactions were expected. Ibandronate is eliminated unchanged by the kidneys. Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system. No clinically significant drug-drug interactions have been detected.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.4 Pediatrics

The applicant requested a waiver for conducting pediatric studies for the proposed indication because post-menopausal osteoporosis does not affect the pediatric population. Pediatric waivers were granted for the original NDA and the once-monthly dose supplement application in 2002 and 2004, respectively.

*Comment: I recommend granting the pediatric waiver because the indication does not affect the pediatric population.*

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The applicant demonstrated efficacy of ibandronate 150 mg monthly in the prevention of postmenopausal osteoporosis by meeting the pre-specified endpoint of Study BA18492. The mean percentage change from baseline in lumbar BMD density after one year of treatment was 3.73% for 68 subjects treated with ibandronate, compared with -0.39% for 70 subjects treated with placebo. The p-value for the comparison was less than 0.0001.

Overall, the safety data provided support for strengthening existing warnings in labeling related to upper gastrointestinal effects and musculoskeletal pain. Current labeling reports that these effects are “infrequent” and have only been reported “postmarketing.” In postmenopausal women, the high level of background noise for gastrointestinal and musculoskeletal complaints obscures a safety signal when common adverse events occurring over a one year period are compared between placebo and treatment groups. However, analysis of adverse events that

occur within five days of dosing, and analysis of challenge-rechallenge data reveals a connection between certain gastrointestinal symptoms, diffuse muscle pain, and ibandronate intake. Labeling should be strengthened accordingly. No new safety issues emerged from the data provided in the submission.

## **9.2 Recommendation on Regulatory Action**

I recommend approval of the supplement pending agreement on final labeling.

## **9.3 Recommendation on Postmarketing Actions**

### *9.3.1 Risk Management Activity*

Postmarketing surveillance is ongoing for the product and should continue.

### *9.3.2 Required Phase 4 Commitments*

I do not recommend any required Phase 4 commitments.

### *9.3.3 Other Phase 4 Requests*

I have no additional Phase 4 requests.

## **9.4 Labeling Review**

The applicant added new text to labeling related to Study BA18492, and converted the labeling into the currently recommended format (21CFR §201.56 and §201.57).

In general, the labeling changes were acceptable. Most of my labeling recommendations were minor grammatical or plain language recommendations. In addition, I recommend strengthening the safety language in the WARNINGS AND PRECAUTIONS Section of labeling by words “postmarketing” and “infrequent.”

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/s/

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Lesley-Anne Furlong  
11/12/2008 10:24:51 PM  
MEDICAL OFFICER

Lisa Soule  
11/13/2008 01:55:41 PM  
MEDICAL OFFICER  
I concur with Dr. Furlong's conclusions and recommendations.



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1 BA18492 Indication: prevention of osteoporosis in postmenopausal women  Pivotal Study #2 Indication:	x			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Study data entirely from U.S. subjects
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			x	
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?			x	Already approved product
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	Protocol was the subject of discussion and agreement with the Division of Metabolic and Endocrine Products.

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?		x		Not required by regulation or needed by reviewer. Adverse events are coded in MedDRA terms. MedDRA dictionary is available on reviewer's computer.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Serious adverse events not requested by the Division.
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	There were no pre-submission discussions with the Division.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver requested because indication does not affect the pediatric population.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	No foreign data.
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				Datasets are available; cannot yet say if all datasets are complete at this point in my review.
34.	Are all datasets to support the critical safety analyses available and complete?				Datasets are available; have been able to find needed datasets to this

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					point in review; cannot say if all datasets are available and complete.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				See statistical filing review.
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			Serious adverse events are not required and were not submitted.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

I have not identified any potential review issues to be forwarded to the applicant for the 74-day letter.

Lesley-Anne Furlong  
 \_\_\_\_\_  
 Reviewing Medical Officer

5-Mar-2008  
 \_\_\_\_\_  
 Date

\_\_\_\_\_  
 Clinical Team Leader

\_\_\_\_\_  
 Date

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

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/s/

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Lesley-Anne Furlong  
3/12/2008 02:52:02 PM  
MEDICAL OFFICER

Lisa Soule  
3/12/2008 03:01:34 PM  
MEDICAL OFFICER  
I concur with Dr. Furlong's conclusions.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**CHEMISTRY REVIEW(S)**

<b>CHEMIST'S REVIEW</b>		
<b>1. ORGANIZATION</b> CDER/ONDQA Division of Post-Marketing Evaluation HFD-580		<b>2. NDA #</b> 21-455 Original NDA approved:
<b>3. NAME AND ADDRESS OF APPLICANT</b> Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110		<b>4. SUPPLEMENT</b> SE1-007 25-JAN-2008 (Rec. 28-JAN-2008)
		<b>5. Name of the Drug</b> Boniva
		<b>6. Nonproprietary Name</b> Ibandronate sodium
<b>7. SUPPLEMENT PROVIDES</b> for safety and efficacy of ibandronate's 150 mg once monthly oral tablet in the prevention of PMO based on data from the single Phase 4 Study BA18492.		<b>8. AMENDMENT</b> --
<b>9. PHARMACOLOGICAL CATEGORY</b> Post-menopausal osteoporosis (PMO)	<b>10. HOW DISPENSED</b> Rx	<b>11. RELATED</b>
<b>12. DOSAGE FORM</b> Tablet, film coated	<b>13. POTENCY</b> 2.5 mg, 150 mg	
<b>CHEMICAL NAME AND STRUCTURE</b> The chemical name for ibandronate sodium is 3-( <i>N</i> -methyl- <i>N</i> -pentyl) amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate with the molecular formula $C_9H_{22}NO_7P_2Na \cdot H_2O$ and a molecular weight of 359.24. 		
<b>15. COMMENTS</b> This is an SE1 Supplement, therefore, there are no changes to Module 3 regarding manufacture of the Drug Product. Only the CMC section of the label was reviewed. The Sponsor was notified by the OND PM to change the designation in the SPL for Score: the acceptable designation for 'no score' is '1'. EA consult and Micro consult not necessary.		
<b>16. CONCLUSIONS AND RECOMMENDATIONS</b> The labeling was provided as proposed (clean) and currently approved (annotated) versions in SPL format as required in the PLR (21 CFR 201.56 & 57). The PLR coding was reviewed. The Highlights of Prescribing Information, Dosage Forms and Strengths (section 3) Description (section 11), How Supplied/Storage and Handling (section 16), and Patient Information sections of the labeling were reviewed. There are no CMC changes. From a CMC perspective, this Supplement can be Approved. OND will issue the Action Letter.		
<b>17. REVIEWER NAME (AND SIGNATURE)</b> Sharon Kelly, PhD		<b>DATE COMPLETED</b> 16-OCT-2008
<b>R/D INITIATED BY</b>		<b>filename:</b> 21-455#007 NDA
<b>DISTRIBUTION:</b> Original: NDA 21-455#007 cc: Division File CSO Reviewer		

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/s/

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Sharon Kelly  
10/23/2008 11:50:56 AM  
CHEMIST

Hasmukh Patel  
10/23/2008 01:27:35 PM  
CHEMIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**PHARMACOLOGY REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

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NDA: 21-455/ SE1-007	Submission Date(s): January 25, 2008
Brand Name	Boniva®
Generic Name	Ibandronate Sodium
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3 (DCP3)
OND division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Hoffman-La Roche
Relevant IND	50,378
Submission Type	Standard
Formulation; Strength	Tablets; 150 mg
Indication	Prevention of Osteoporosis

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In this efficacy supplement, the sponsor sought the approval of the 150 mg once monthly tablet formulation of Ibandronate in the prevention of osteoporosis. There is no new Clinical Pharmacology information included with this submission.

The revised labeling submitted in the Physician's Labeling Rule (PLR) format has been reviewed by Office of Clinical Pharmacology (OCP) and a brief memo was entered into DFS that found the NDA supplement to be acceptable pending agreement on labeling (see DFS review dated 07/16/2008).

This memo serves to confirm that the revised labeling (dated 11.21.08) has been reviewed by OCP and the sNDA is therefore acceptable from a Clinical Pharmacology perspective.

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11/25/2008 01:21:04 PM  
BIOPHARMACEUTICS

MEMO

FOOD AND DRUG ADMINISTRATION

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**Division of Reproductive and Urologic Products  
Center for Drug Evaluation and Research**

**Date:** November 21, 2008

**Reviewer:** Lynnda Reid, Ph.D., Supervisory Pharmacologist, DRUP

**NDA #/SS#/date:** 21-455 (S007) 1/28/2008

**Sponsor:** Hoffmann-La Roche, Inc.

**Drug Product:** Boniva (ibandronate sodium 150 mg) Tablets

**Indication:** Prevention of Osteoporosis in postmenopausal women

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**Background:** The original pharmacology/toxicology review for this submission (S007) was filed on October 15, 2008. At that time, the only outstanding issue was labeling. The Sponsor has submitted the final label for review on November 21, 2008.

**Conclusion/Recommendation:** Submitted labeling is acceptable from a Pharmacology/Toxicology perspective. Nonclinical data support approval of this supplement.

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/s/

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Lynnda Reid  
11/21/2008 01:23:38 PM  
PHARMACOLOGIST



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

**NDA NUMBER:** 21-455  
**SERIAL NUMBER:** 007  
**DATE RECEIVED BY CENTER:** 1/28/2008  
**PRODUCT:** Boniva (ibandronate sodium 150 mg) Tablets  
**INTENDED CLINICAL POPULATION:** Prevention of Osteoporosis in postmenopausal women  
**SPONSOR:** Hoffmann-La Roche, Inc.  
**DOCUMENTS REVIEWED:** Labeling  
**REVIEW DIVISION:** Division of Reproductive and Urologic Products  
**PHARM/TOX REVIEWER:** Lynnda Reid, Ph.D., Supervisory Pharmacologist  
**DIVISION DIRECTOR:** Scott Monroe, M.D.  
**PROJECT MANAGER:** Karl Stiller

**Date of review submission to Division File System (DFS):** October 15, 2008

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## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

- A. Recommendation on approvability: Nonclinical data support approval.
- B. Recommendation for nonclinical studies: None
- C. Recommendations on labeling: The latest approved label on February 13, 2007, adequately reflects the nonclinical safety/toxicology data for ibandronate sodium. Recommended changes to Sections 8.1 and 13.2 reflect current recommendations for format and content for animal reproductive and developmental findings for these sections. Detailed recommendations can be found on page 9.

### **II. Summary of nonclinical findings**

- A. Brief overview of nonclinical findings:
- B. Pharmacologic activity: Ibandronate is a nitrogen-containing bisphosphonate which inhibits osteoclast-mediated bone resorption. This inhibition indirectly suppresses bone formation and ultimately leads to an inhibition of bone turnover. In postmenopausal women bone loss is accelerated due to increased activation of basic multicellular units (BMU's) and a negative balance between bone formation and resorption in each remodeling cycle. Ibandronate and other bisphosphonates prevent or reverse this bone loss by reducing the size of the remodeling space at the tissue level, and increasing the degree of mineralization and increase focal bone balance in each newly formed bone unit.
- C. Nonclinical safety issues relevant to clinical use:

*Renal Toxicity:* Bisphosphonate-induced renal failure in rats, dogs and monkeys is most likely associated with degenerative tubule lesions at relatively low doses of ibandronate (6 times the recommended 150 mg monthly dose). Adverse renal effects were dependent on both AUC and infusion rate (i.e. C<sub>max</sub>). Although exposure margins are reasonable, the high inter-patient variability in plasma exposure to ibandronate with oral treatment, resulting from variable absorption and elimination, suggests that renal safety may be an issue for some patients exposed to monthly 150 mg oral doses.

*Liver toxicity:* Indicators of liver toxicity were observed in repeat dose IV and oral studies, i.e., increased liver enzymes, AST and ALT (rat and dog), congestion and necrosis (rat) and vacuolation (dog). Exposures were 10 times higher in the rat, and 25 times higher in the dog compared to human AUC levels following the 150 mg monthly dose.

*Gastrointestinal toxicity:* GI effects were observed in IV and oral studies in dogs and rats. Since the characterization of liver and GI toxicity in animals was done by IV or daily oral dosing the data are not an ideal support for the proposed clinical dose regimen (monthly dosing with relatively high oral dose).

*Reproductive toxicology:* In reproductive toxicity studies in the rat, ibandronate caused severe maternal dystocia and maternal and fetal periparturient mortality at doses in the range of human exposure, given either before or during delivery. This effect has been observed with other bisphosphonates and is believed to be result of hypocalcemia due to suppression of skeletal calcium mobilization required for delivery in the rat.

In rats, ibandronate is transferred across the placenta and excreted in milk.

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 21-455

**Sequence number/date/type of submission:** N007, SE1, 1/28/2008

**Information to sponsor:** Yes ( ) No ( x )

**Sponsor and/or agent:** Hoffmann-La Roche, Inc.

**Reviewer name:** Lynnda Reid

**Division name:** Division of Reproductive and Urologic Products

**HFD #:** 580

**Review completion date:** 10/1/08

#### Drug:

**Trade name:** Boniva\_

**Generic name:** Ibandronate sodium

**Code name:** BM21.09955.Na.H2O

**Chemical name:** [1-hydroxy-3-(methylpentylamino) propylidene] bisphosphonic acid, monosodium salt, monohydrate

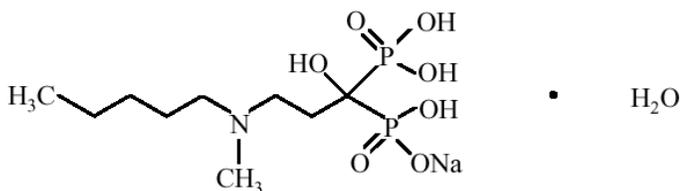
**CAS registry number:** 114084-78-5

**Molecular formula:** C<sub>9</sub>H<sub>22</sub>NO<sub>7</sub>P<sub>2</sub>Na.H<sub>2</sub>O

**Molecular weight:** Mw 359.2 (sodium salt), 319.2 (free acid)

**Conversions:** 1 mg P= 5.14 mg free acid; 1 g free acid equivalent = 1.125 g ibandronate monosodium salt, monohydrate)

**Structure:**



**Relevant INDs/NDAs/DMFs:** IND 46,266, IND 50,378, DMF 15429

**Drug class:** Bisphosphonate (bone resorption inhibitor)

**Intended clinical population:** Prevention of Osteoporosis in postmenopausal women

**Clinical formulation:** Film-coated tablet, containing 1.68.75 mg ibandronate monosodium hydrate (150 mg free acid), lactose monohydrate, povidone, cellulose, crospovidone, stearic acid, silicon dioxide, and water.

**Route of administration:** Oral (tablet)

**Data reliance:** Except as specifically identified below, all data and information discussed below and necessary for approval of [REDACTED]<sup>(b) (4)</sup> are owned by the Applicant.

Ibandronate (BONIVA®) 2.5 mg oral daily doses were approved for the treatment and prevention of postmenopausal osteoporosis in May, 2003. In March, 2005, the once monthly dose of 150 mg was approved for the **treatment** of postmenopausal osteoporosis.

This supplemental application (SE1/007) was filed to demonstrate safety and efficacy of once monthly oral ibandronate 150 mg in the **prevention** of postmenopausal osteoporosis.

The following information is from the Pharmacology/Toxicology data reviewed by Dr. Gemma Kuipers in support of the original 150 mg dose approved for the treatment of postmenopausal osteoporosis.

## 2.6.2 PHARMACOLOGY

### 2.6.2.1 Brief summary

Ibandronate, a nitrogen-containing bisphosphonate with high affinity for hydroxyapatite, has been shown to inhibit osteoclast-mediated bone resorption. This inhibition indirectly suppresses bone formation and ultimately leads to an inhibition of bone turnover. In postmenopausal women bone loss is accelerated due to increased activation of basic multicellular units (BMU's) and a negative balance between bone formation and resorption in each remodeling cycle. Ibandronate and other bisphosphonates prevent or reverse this bone loss by reducing the size of the remodeling space at the tissue level, and increasing the degree of mineralization and increase focal bone balance in each newly formed bone unit. This results in an increase in bone volume and bone mass as reflected by an increase in bone mineral density (BMD).

Nonclinical efficacy pharmacology studies were carried out to investigate the effect of ibandronate in animal models of nonstimulated or stimulated bone turnover. Data from rat studies showed that ibandronate inhibited bone resorption, and is approximately 10x, 50-100x, and 500x more potent than alendronate, pamidronate and clodronate, respectively. In the intact growing rat, ibandronate had a prolonged inhibitory effect and increased cancellous bone volume and density with an optimal dose  $\geq 0.001$  mg/kg. Mineralization was not affected at doses 1000-5000x times higher than the doses optimally inhibiting bone resorption and turnover, based on data from the intact growing rat and the aged ovariectomized rat.

Long-term pharmacology studies on the effects of ibandronate on bone quality in estrogen deficient animals were the most relevant studies for the postmenopausal osteoporosis indication. In rats and monkeys, continuous or intermittent dosing for 12 to 16 months prevented the loss of bone induced by ovariectomy (OVX) through inhibition of bone resorption and turnover. At optimal dose levels vertebral bone strength was preserved in parallel with BMD, histologic bone

volume and trabecular structure. In the OVX rat, ibandronate also protected femoral cortical bone BMD and strength. In OVX monkeys, ibandronate fully preserved BMD at the ulna and femoral neck, but bone strength at those sites was not significantly protected. This may have been due to relative inefficacy of ibandronate to protect against cortical thinning or other structural effects resulting from estrogen deficiency not reflected by BMD, or to methodological variability. In the monkey study, significant positive correlations between BMD and strength of vertebrae and femoral neck and between BMC and strength of ulna diaphysis were demonstrated. There was no indication that the relation between BMD and bone strength was eliminated when dosing was carried out in intermittent fashion. Although the efficacy of ibandronate to preserve bone strength at cortical or mixed cortical/cancellous sites appeared to be limited, the animal data do not predict an adverse effect on bone strength. There were no deleterious effects on bone histology or mineralization in all animal species tested.

### **2.6.2.2 Primary pharmacodynamics**

Mechanism of action: inhibit osteoclast-mediated bone resorption

Drug activity related to proposed indication: inhibition of bone resorption indirectly suppresses bone formation and ultimately leads to an inhibition of bone turnover

### **2.6.2.3 Secondary pharmacodynamics**

#### **2.6.2.4 Safety pharmacology**

Single dose safety pharmacology studies in mice, rats or dogs showed that ibandronate did not affect CNS, gastrointestinal, cardiovascular or renal function at doses of 100-2000 times the intended human 2.5 mg/day dose, based on body surface area comparison (mg/m<sup>2</sup>). Ibandronate did not affect in vitro hERG K<sup>+</sup> channel currents at >200x a human C<sub>max</sub> of 50 ng/ml following ibandronate 3 x 50 mg or 1 x 150 mg.

### **2.6.3 PHARMACOLOGY TABULATED SUMMARY**

[none submitted]

### **2.6.4 PHARMACOKINETICS/TOXICOKINETICS**

#### **2.6.4.1 Brief summary**

In rats and dogs, ibandronate was poorly absorbed after oral administration (1% of dose or less) and food markedly suppressed oral bioavailability. After oral administration, T<sub>max</sub> is 0.5-1 h and compound is rapidly cleared (within hours) from plasma by uptake in bone and renal excretion. T<sub>1/2</sub> (oral or i.v.) is approximately 56 hours in the dog. Bioavailability after s.c. administration is 100% in the rat. Uptake in the bone compartment is reflected by a high volume of distribution (10L/kg in dogs). Approximately 40-50% of an absorbed dose is taken up and stored by bone, and approximately 50% is eliminated unchanged via the kidney. Uptake in bone is linear and related to total dose rather than treatment schedule. Bone levels attained after even a single dose remain high for several months, and T<sub>1/2</sub> for bone tissue in the rat is 400-500

days. Ibandronate is accumulated in spleen, kidney and liver tissue, but does not cross the blood-brain barrier. In pregnant rats, ibandronate is distributed to the placenta and the fetus, and in lactating rats it is excreted in the milk. Binding to plasma proteins is similar for rat, dog and human (80-99%). There is no evidence for metabolism in rats or dogs, and no evidence for hepatic or renal drug-drug interaction.

## 2.6.5 PHARMACOKINETICS TABULATED SUMMARY

[none provided]

## 2.6.6 TOXICOLOGY

### 2.6.6.1 Overall toxicology summary

General toxicology: Acute toxicity studies in mice, rats, and dogs revealed toxicities to CNS, GI tract, liver, lung and kidney. The lowest exposure multiple (based on mg/m<sup>2</sup>) was 20x in oral rat study (GI tract edema, dilation, hemorrhage). Liver congestion in the oral mouse study was seen at 56x human dose (mg/m<sup>2</sup> basis).

Oral gavage toxicity studies with daily dosing for up to 12-month duration were performed in rats and dogs. Target organs identified in the daily studies were kidney, liver, lung, esophagus, stomach, thymus and testes. Renal tubular integrity was especially sensitive to ibandronate in rats and dogs.

IV toxicity studies of up to 6 months in duration with daily or biweekly dosing were carried out in rats and dogs. Exposure multiples based on IV animal studies were calculated on the basis of AUC comparison. The C<sub>max</sub>/AUC ratio in rats and dogs dosed with bolus IV injections is approximately 1/1. With 15- to 60-minute IV infusions the ratio is lower, and at 60-minutes it is relatively similar to that with oral dosing in humans (1/4). Thus, exposure (AUC) attained in IV studies generally serves as an adequate basis for calculating exposure multiples based on the NOAEL dose in animals.

*Renal Toxicity*: Bisphosphonate-induced renal failure is most likely associated with degenerative tubule lesions such as those observed in the rat. IV studies showed that a variety of histologic renal lesions are induced by relatively low doses of ibandronate, and that most lesions are dependent on both AUC and infusion rate (i.e. C<sub>max</sub>). In the intermittent monthly IV dosing study with 9 doses of 1 mg/kg, the most sensitive histologic parameters of renal damage were degeneration and necrosis in the proximal convoluted tubule, and hypertrophy and hyperplasia of the distal tubules.

The IV studies provided the most relevant information on NOAEL's for the renal lesions. Exposure multiples based on NOAEL for this renal lesion and AUC comparison in rats and humans treated with the monthly oral 150 mg dose (200 ng·h/mL) were approximately 6 fold. Exposure multiples for the hypertrophy of distal parts of the renal tubules and collecting ducts were similar (6x). Based on data from IV dog studies, the exposure multiples for renal histologic lesions and functional toxicity were also 6-7 fold. Although the margins from the intermittent IV studies were most relevant for the proposed monthly clinical treatment regimen, exposure multiples based on AUC data from chronic daily oral studies were also determined. Without

correction for dosing frequency they were relatively low (rat: 0.1x-0.7x, dog: 1.7x), but they were acceptable when based on cumulative monthly doses.

The OVX monkey bone pharmacology study also provided a 6 fold exposure multiples for renal toxicity. Although these margins are reasonable, the high inter-patient variability in plasma exposure to ibandronate with oral treatment, resulting from variable absorption and elimination, suggests that renal safety may be an issue for some patients exposed to monthly 150 mg oral doses.

*Liver toxicity:* Indicators of liver toxicity were observed in repeat dose IV and oral studies, i.e., increased liver enzymes, AST and ALT (rat and dog), congestion and necrosis (rat) and vacuolation (dog). Exposure multiples based on AUC comparison were >10x (rat), and  $\geq$ 25x (dog). It was unclear whether liver toxicity in animals was different between IV and oral dosing regimens.

*Gastrointestinal toxicity:* GI effects were observed in weekly IV and oral studies in dogs, and daily oral studies in rat. Exposure multiples based on the NOAEL for the dog were 25 fold in the IV study, and 48 fold based on monthly exposure in the daily oral study. However, they were much lower in a 7-day study in the dog with daily 50 mg tablets (0.3-1.7x). For the rat, the exposure multiple based on the NOAEL with daily oral treatment translated to 12-18 fold based on 30-day cumulative exposure. Since the characterization of liver and GI toxicity in animals was done by IV or daily oral dosing the data are not an ideal support for the proposed clinical dose regimen (monthly dosing with relatively high oral dose).

*Bone Effects:* Pharmacodynamic effects of ibandronate on bone were observed in all rat and dog toxicity studies at low human exposure multiples. This led to secondary effects of decreased bone marrow space and increased extramedullary hematopoiesis, and at higher doses to anemia.

*Other:* Lung, thymus and testicular effects observed in the weekly IV dog study were associated with exposure multiples of 13-48 fold.

Genetic toxicology: Ibandronate had no mutagenic or clastogenic potential, as demonstrated by in vitro and in vivo negative genotoxicity assays.

Carcinogenicity: Carcinogenicity studies in rats and mice dosed daily via oral gavage for 18-24 months did not show an increased incidence of tumors. Cumulative monthly exposure multiples achieved in the rat and mouse oral gavage studies were 3.5x and 2x for male and female rats, and 135x and 20x for male and female mice, respectively, as compared to exposure at the 150 mg oral clinical dose (AUC). However, in a carcinogenicity study in mice dosed daily via the drinking water for 90 weeks, an increase in the incidence of adrenal subcapsular adenoma was observed in females at high human exposure multiples (cumulative monthly exposure 115 times human exposure at the 150 mg oral clinical dose, based on AUC).

Reproductive toxicology: In reproductive toxicity studies in the rat, ibandronate caused severe maternal dystocia and maternal and fetal periparturient mortality at doses in the range of human exposure, given either before or during delivery. This effect has been observed with other bisphosphonates and is believed to be result of hypocalcemia due to suppression of skeletal calcium mobilization required for delivery in the rat. Effects on fertility and a fetal kidney anomaly (RPU syndrome) were observed at relatively high human exposure multiples (13x and 9x, based on the monthly 150 mg oral clinical dose). An effect of treatment on a pup behavioral

developmental parameter (cliff avoidance) was observed when dams were dosed from 14 days before gestation at high human exposure multiples (13x). In the rabbit, no teratogenic effects were identified at human dose (mg/m<sup>2</sup>) multiples of 4x-80x. In rats, ibandronate is transferred across the placenta and excreted in milk. Multiples are based on the 150 mg oral clinical dose.

## 2.6.7 TOXICOLOGY TABULATED SUMMARY

[none provided]

## OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The data from pharmacology and toxicology studies suggest adequate safety of long term use of ibandronate for the treatment or prevention of osteoporosis in postmenopausal women at an oral dose of 150 mg once monthly.

Unresolved toxicology issues (if any): None

Recommendations: None

Suggested labeling: To be consistent with other bisphosphonate labels, I recommend that the class labeling for bisphosphonates regarding potential reproductive risks be moved to the beginning of the Pregnancy section 8.1. The move of the detailed animal data (containing animal doses and the bases of calculated dosing multiples) from Section 8.1 to Section 13.2 is also consistent with current labeling format recommendations made by the Maternal Health Team.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 PREGNANCY: CATEGORY C

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

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

In female rats given ibandronate orally at doses  $\geq 3$  times human exposure at the recommended daily oral dose of 2.5 mg or  $\geq 1$  times human exposure at the recommended once-monthly oral dose of 150 mg beginning 14 days before mating and continuing through lactation, maternal deaths were observed at the time of delivery in all dose groups. Perinatal pup loss in dams given 45 times human exposure at the recommended daily dose and 13 times the recommended once-monthly dose was likely related to maternal dystocia. Calcium supplementation did not completely prevent dystocia and periparturient mortality in any of the treated groups at  $\geq 16$  times the recommended daily dose and  $\geq 4.6$  times the recommended once-monthly dose. A low incidence of postimplantation loss was observed in rats treated from 14 days before mating throughout lactation or during gestation, only at doses causing maternal dystocia and periparturient mortality. In pregnant rats dosed orally from gestation day 17 through lactation day 21 (following closure of the hard palate through weaning), maternal toxicity, including dystocia and mortality, fetal perinatal and postnatal mortality, were observed at doses equivalent to human exposure at the recommended daily and  $\geq 4$  times the recommended once-monthly dose. Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia. (b) (4)

Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at oral doses 30 times the human exposure at the recommended daily oral dose of 2.5 mg and  $\geq 9$  times the recommended once-monthly oral dose of 150 mg. Impaired pup neuromuscular development (cliff avoidance test) was observed at 45 times human exposure at the daily dose and 13 times the once-monthly dose. (b) (4)

In pregnant rabbits treated orally with ibandronate during gestation at doses  $\geq 8$  times the recommended human daily oral dose of 2.5 mg and  $\geq 4$  times the recommended human once-monthly oral dose of 150 mg, dose-related maternal mortality was observed in all treatment groups. The deaths occurred prior to parturition and were associated with lung edema and hemorrhage. No significant fetal anomalies were observed. (b) (4)

(b) (4)

### 8.3 NURSING MOTHERS

In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast milk [REDACTED] (b) (4) from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. [REDACTED] (b) (4)

## 13 NONCLINICAL TOXICOLOGY

### 13.1 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

#### Carcinogenesis

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

#### Mutagenesis

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

#### Impairment of Fertility

In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed at an oral dose of 16 mg/kg/day (45 times human exposure at the recommended daily oral dose of 2.5 mg and

13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison).

### **13.2 ANIMAL REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY**

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

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

In pregnant rabbits given oral doses of 1, 4, or 20 mg/kg/day during gestation, dose-related maternal mortality was observed in all treatment groups ( $\geq 8$  times the recommended human daily oral dose of 2.5 mg and  $\geq 4$  times the recommended human once-monthly oral dose of 150 mg, based on body surface area comparison,  $\text{mg}/\text{m}^2$ ). The

deaths occurred prior to parturition and were associated with lung edema and hemorrhage. No significant fetal anomalies were observed.

(b) (4)

### **13.23 ANIMAL PHARMACOLOGY**

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

Long-term daily or once-monthly intermittent administration of ibandronate to ovariectomized rats or monkeys was associated with suppression of bone turnover and increases in bone mass. In both rats and monkeys, vertebral BMD, trabecular density, and biomechanical strength were increased dose-dependently at doses up to 15 times the recommended human daily oral dose of 2.5 mg, or cumulative monthly doses up to 8 times (rat) or 6 times (monkey) the recommended human once-monthly oral dose of 150 mg, based on body surface area ( $\text{mg}/\text{m}^2$ ) or AUC comparison. In monkeys, ibandronate maintained the positive correlation between bone mass and strength at the ulna and femoral neck. New bone formed in the presence of ibandronate had normal histologic structure and did not show mineralization defects.

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Lynnda Reid  
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PHARMACOLOGIST

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 21-455

**Applicant:** Hoffmann-La Roche, Inc.    **Stamp Date:** 1/28/08

**Drug Name:** Boniva (ibandronate sodium) Tablets    **NDA/BLA Type:** NDA SE1/007

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	NA		All nonclinical data is cross-referenced to IND 50,378 and previous NDA 21-455 submissions. This submission does not include any new nonclinical data.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	NA		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	NA		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		All nonclinical studies necessary for prior approval of the once monthly 150 mg dose of ibandronate have been previously reviewed. No new nonclinical issues have been identified since marketing.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	NA		This is an already approved formulation: Boniva® (150 mg ibandronate sodium) Tablets.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	NA		

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Labelin Labeling has been submitted in PLR format. Significant labeling revisions will be recommended to conform to current SEALD labeling recommendations for sections 8.1 and 13.2.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	NA		
11	Has the applicant addressed any abuse potential issues in the submission?	NA		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	NA		

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?** Yes

**Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.** None

**Expected Review Completion Date:** Prior to Mid-Cycle Meeting

**Introduction:** Ibandronate (BONIVA®) 2.5 mg oral daily doses were approved for the treatment and prevention of postmenopausal osteoporosis in May, 2003. In March, 2005, the once monthly dose of 150 mg was approved for the treatment of postmenopausal osteoporosis.

This supplemental application (SE1/007) was filed to demonstrate safety and efficacy of once monthly oral ibandronate 150 mg in the prevention of postmenopausal osteoporosis.

The following information is from the Pharmacology/Toxicology data reviewed by Dr. Gemma Kuipers in support of the original 150 mg dose approved for the treatment of postmenopausal osteoporosis.

**Pharmacology:** Ibandronate, a nitrogen-containing bisphosphonate with high affinity for hydroxyapatite, has been shown to inhibit osteoclast-mediated bone resorption. This inhibition indirectly suppresses bone formation and ultimately leads to an inhibition of bone turnover. In postmenopausal women bone loss is accelerated due to increased activation of basic multicellular units (BMU's) and a negative balance between bone formation and resorption in each remodeling cycle. Ibandronate and other bisphosphonates prevent or reverse this bone loss by reducing the size of the remodeling space at the tissue level, and increasing the degree of mineralization and increase focal bone balance in each newly formed bone unit. This results in an increase in bone volume and bone mass as reflected by an increase in bone mineral density (BMD).

Nonclinical efficacy pharmacology studies were carried out to investigate the effect of ibandronate in animal models of nonstimulated or stimulated bone turnover. Data from rat studies showed that ibandronate inhibited bone resorption, and is approximately 10x, 50-100x, and 500x more potent than alendronate, pamidronate and clodronate, respectively. In the intact growing rat, ibandronate had a prolonged inhibitory effect and increased cancellous bone volume and density with an optimal dose  $\geq 0.001$  mg/kg. Mineralization was not affected at doses 1000-5000x times higher than the doses optimally inhibiting bone resorption and turnover, based on data from the intact growing rat and the aged ovariectomized rat.

Long-term pharmacology studies on the effects of ibandronate on bone quality in estrogen deficient animals were the most relevant studies for the postmenopausal osteoporosis indication. In rats and monkeys, continuous or intermittent dosing for 12 to 16 months prevented the loss of bone induced by ovariectomy (OVX) through inhibition of bone resorption and turnover. At optimal dose levels vertebral bone strength was preserved in parallel with BMD, histologic bone volume and trabecular structure. In the OVX rat, ibandronate also protected femoral cortical bone BMD and strength. In OVX monkeys, ibandronate fully preserved BMD at the ulna and femoral neck, but bone strength at those sites was not significantly protected. This may have been due to relative inefficacy of ibandronate to protect against cortical thinning or other structural effects resulting from estrogen deficiency not reflected by BMD, or to methodological variability. In the monkey study, significant positive correlations between BMD and strength of vertebrae and femoral neck and between BMC and strength of ulna diaphysis were demonstrated. There was no indication that the relation between BMD and bone strength was eliminated when dosing was carried out in intermittent fashion. Although the efficacy of ibandronate to preserve bone strength at cortical or mixed cortical/cancellous sites appeared to be limited, the animal data do not predict an adverse effect on bone strength. There were no deleterious effects on bone histology or mineralization in all animal species tested.

**Safety Pharmacology:** Single dose safety pharmacology studies in mice, rats or dogs showed that ibandronate did not affect CNS, gastrointestinal, cardiovascular or renal function at doses of 100-2000 times the intended human 2.5 mg/day dose, based on body surface area comparison (mg/m<sup>2</sup>). Ibandronate did not affect in vitro hERG K<sup>+</sup> channel currents at  $>200$ x a human C<sub>max</sub> of 50 ng/ml following ibandronate 3 x 50 mg or 1 x 150 mg.

**Pharmacokinetics:** In rats and dogs, ibandronate was poorly absorbed after oral administration (1% of dose or less) and food markedly suppressed oral bioavailability. After oral administration, T<sub>max</sub> is 0.5-1 h and compound is rapidly cleared (within hours) from plasma by uptake in bone and renal excretion. T<sub>1/2</sub> (oral or i.v.) is approximately 56 hours in the dog. Bioavailability after s.c. administration is 100% in the rat. Uptake in the bone compartment is reflected by a high volume of distribution (10L/kg in dogs). Approximately 40-50% of an absorbed dose is taken up and stored by bone, and approximately 50% is eliminated unchanged via the kidney. Uptake in bone is linear and related to total dose rather than treatment schedule. Bone levels attained after even a single dose remain high for several months, and T<sub>1/2</sub> for bone tissue in the rat is 400-500 days. Ibandronate is accumulated in spleen, kidney and liver tissue, but does not cross the blood-brain barrier. In pregnant rats, ibandronate is distributed to the placenta and the fetus, and in lactating rats it is excreted in the milk. Binding to plasma proteins is similar for rat, dog and human (80-99%). There is no evidence for metabolism in rats or dogs, and no evidence for hepatic or renal drug-drug interaction.

**Toxicology:** Acute toxicity studies in mice, rats, and dogs revealed toxicities to CNS, GI tract, liver, lung and kidney. The lowest exposure multiple (based on mg/m<sup>2</sup>) was 20x in oral rat study

(GI tract edema, dilation, hemorrhage). Liver congestion in the oral mouse study was seen at 56x human dose (mg/m<sup>2</sup> basis).

Oral gavage toxicity studies with daily dosing for up to 12-month duration were performed in rats and dogs. Target organs identified in the daily studies were kidney, liver, lung, esophagus, stomach, thymus and testes. Renal tubular integrity was especially sensitive to ibandronate in rats and dogs.

IV toxicity studies of up to 6 months in duration with daily or biweekly dosing were carried out in rats and dogs. Exposure multiples based on IV animal studies were calculated on the basis of AUC comparison. The C<sub>max</sub>/AUC ratio in rats and dogs dosed with bolus IV injections is approximately 1/1. With 15- to 60-minute IV infusions the ratio is lower, and at 60-minutes it is relatively similar to that with oral dosing in humans (1/4). Thus, exposure (AUC) attained in IV studies generally serves as an adequate basis for calculating exposure multiples based on the NOAEL dose in animals.

Renal Toxicity: Bisphosphonate-induced renal failure is most likely associated with degenerative tubule lesions such as those observed in the rat. IV studies showed that a variety of histologic renal lesions are induced by relatively low doses of ibandronate, and that most lesions are dependent on both AUC and infusion rate (i.e. C<sub>max</sub>). In the intermittent monthly IV dosing study with 9 doses of 1 mg/kg, the most sensitive histologic parameters of renal damage were degeneration and necrosis in the proximal convoluted tubule, and hypertrophy and hyperplasia of the distal tubules.

The IV studies provided the most relevant information on NOAEL's for the renal lesions. Exposure multiples based on NOAEL for this renal lesion and AUC comparison in rats and humans treated with the monthly oral 150 mg dose (200 ng-h/mL) were approximately 6 fold. Exposure multiples for the hypertrophy of distal parts of the renal tubules and collecting ducts were similar (6x). Based on data from IV dog studies, the exposure multiples for renal histologic lesions and functional toxicity were also 6-7 fold. Although the margins from the intermittent IV studies were most relevant for the proposed monthly clinical treatment regimen, exposure multiples based on AUC data from chronic daily oral studies were also determined. Without correction for dosing frequency they were relatively low (rat: 0.1x-0.7x, dog: 1.7x), but they were acceptable when based on cumulative monthly doses.

The OVX monkey bone pharmacology study also provided a 6 fold exposure multiples for renal toxicity. Although these margins are reasonable, the high inter-patient variability in plasma exposure to ibandronate with oral treatment, resulting from variable absorption and elimination, suggests that renal safety may be an issue for some patients exposed to monthly 150 mg oral doses.

Liver toxicity: Indicators of liver toxicity were observed in repeat dose IV and oral studies, i.e., increased liver enzymes, AST and ALT (rat and dog), congestion and necrosis (rat) and vacuolation (dog). Exposure multiples based on AUC comparison were >10x (rat), and ≥25x (dog). It was unclear whether liver toxicity in animals was different between IV and oral dosing regimens.

Gastrointestinal toxicity: GI effects were observed in weekly IV and oral studies in dogs, and daily oral studies in rat. Exposure multiples based on the NOAEL for the dog were 25 fold in the IV study, and 48 fold based on monthly exposure in the daily oral study. However, they were much lower in a 7-day study in the dog with daily 50 mg tablets (0.3-1.7x). For the rat, the

exposure multiple based on the NOAEL with daily oral treatment translated to 12-18 fold based on 30-day cumulative exposure. Since the characterization of liver and GI toxicity in animals was done by IV or daily oral dosing the data are not an ideal support for the proposed clinical dose regimen (monthly dosing with relatively high oral dose).

Bone Effects: Pharmacodynamic effects of ibandronate on bone were observed in all rat and dog toxicity studies at low human exposure multiples. This led to secondary effects of decreased bone marrow space and increased extramedullary hematopoiesis, and at higher doses to anemia.

Other: Lung, thymus and testicular effects observed in the weekly IV dog study were associated with exposure multiples of 13-48 fold.

**Genotoxicity:** Ibandronate had no mutagenic or clastogenic potential, as demonstrated by in vitro and in vivo negative genotoxicity assays.

**Carcinogenicity:** Carcinogenicity studies in rats and mice dosed daily via oral gavage for 18-24 months did not show an increased incidence of tumors. Cumulative monthly exposure multiples achieved in the rat and mouse oral gavage studies were 3.5x and 2x for male and female rats, and 135x and 20x for male and female mice, respectively, as compared to exposure at the 150 mg oral clinical dose (AUC). However, in a carcinogenicity study in mice dosed daily via the drinking water for 90 weeks, an increase in the incidence of adrenal subcapsular adenoma was observed in females at high human exposure multiples (cumulative monthly exposure 115 times human exposure at the 150 mg oral clinical dose, based on AUC).

**Reproductive and Developmental Toxicity:** In reproductive toxicity studies in the rat, ibandronate caused severe maternal dystocia and maternal and fetal periparturient mortality at doses in the range of human exposure, given either before or during delivery. This effect has been observed with other bisphosphonates and is believed to be result of hypocalcemia due to suppression of skeletal calcium mobilization required for delivery in the rat. Effects on fertility and a fetal kidney anomaly (RPU syndrome) were observed at relatively high human exposure multiples (13x and 9x, based on the monthly 150 mg oral clinical dose). An effect of treatment on a pup behavioral developmental parameter (cliff avoidance) was observed when dams were dosed from 14 days before gestation at high human exposure multiples (13x). In the rabbit, no teratogenic effects were identified at human dose (mg/m<sup>2</sup>) multiples of 4x-80x. In rats, ibandronate is transferred across the placenta and excreted in milk. Multiples are based on the 150 mg oral clinical dose.

**CONCLUSION:** The data from pharmacology and toxicology studies suggest adequate safety of long term use of ibandronate for the treatment or prevention of osteoporosis in postmenopausal women at an oral dose of 150 mg once monthly.

Reviewer: Lynnda Reid, Ph.D.  
Supervisory Pharmacologist  
Division of Reproductive and Urologic Products

Date: 3/11/08

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## Clinical Studies

NDA/Serial number            21-455 / SE1-007  
Drug Name:                    Ibandronate (Boniva<sup>™</sup>)  
Indication(s):                Prevention of bone loss in osteopenic women  
Applicant:                     Roche  
Date(s):                        Letter Date 25-Jan 2008  
                                      PDUFA Goal Date 28-Nov-2008  
Review Status:                Standard  
  
Biometrics Division:        DB3  
Statistical Reviewer:        Stella Grosser, Ph.D.  
Concurring Reviewers:      Mahboob Sobhan, Ph.D.  
  
Medical Division:            Division of Reproductive and Urological Products  
Clinical Team:                Lesley-Anne Furlong, M.D., Medical Officer  
                                      Lisa Soule, M.D., Team Leader  
Project Manager:             Karl Stiller  
  
Keywords: NDA review, clinical studies

## **Introduction**

The oral bisphosphonate ibandronate (IBN), with trade name Boniva™, was approved (May 16, 2003) for the treatment and prevention of postmenopausal osteoporosis at a dose of 2.5 mg once daily. IBN 150 mg once monthly was approved (May 16, 2003) for the treatment of postmenopausal osteoporosis.

With this supplemental NDA, the applicant seeks approval of the use of IBN 150 mg once monthly in the prevention of bone loss in osteopenic women. One Phase 3 study, protocol BA18492, was submitted in support of the indication. The application was submitted electronically.

## **Study design**

BA18492 was a double-blind, randomized, placebo-controlled, multicenter study, designed to investigate the efficacy and safety of 1 year of treatment with 150 mg once monthly oral IBN in the prevention of bone loss in postmenopausal osteopenic women. The duration of the study was 12 months.

This study was conducted at 10 centers in the United States. One-hundred and sixty (160) women were randomized; 77 received 150 mg IBN tablet once monthly, 83 received placebo). All subjects received 500 mg calcium and 400 IU of vitamin D. Subjects were stratified by time since menopause (0.5 to 3.0 years and >3.0 years).

*Inclusion criteria:* Subjects were post-menopausal and ambulatory at the beginning of the trial, between the ages of 45 and 60 years old, with baseline mean lumbar spine bone mineral density (BMD) T-score <-1.0 and >-2.5 (L2-L4) and, baseline proximal femur (total hip, trochanter, femoral neck) BMD T-score >-2.5.

To be considered post-menopausal, non-hysterectomized women had to be amenorrheic for at least 12 months prior to study entry or amenorrheic for at least 6 months with serum follicle-stimulating hormone (FSH) levels >50 IU/mL. Hysterectomized women without bilateral oophorectomy prior to menopause had to have serum FSH >50 IU/mL (tested at least 12 months prior to study entry) or have post-surgical bilateral oophorectomy with or without hysterectomy 6 weeks prior to study entry.

### *Efficacy endpoints*

The primary efficacy assessment was the relative change (%) from baseline in mean lumbar spine (L2- L4) BMD at 12 months of treatment.

Secondary assessments included

- Absolute change (g/cm<sup>2</sup>) from baseline in mean lumbar spine (L2-L4) BMD at month 12
- Relative (%) and absolute (g/cm<sup>2</sup>) change in mean BMD from baseline in proximal femur (total hip, trochanter, femoral neck) at month 12

- Percent responders defined as:
  - subjects with mean lumbar spine BMD above or equal to baseline at month 12
  - subjects with proximal femur BMD above or equal to baseline at month 12
  - subjects with both lumbar spine and proximal femur BMD above or equal to baseline at month 12
- Relative (%) and absolute (ng/mL) change from baseline sCTX at months 3, 6, and 12

All measurements of lumbar spine mean BMD used at least two vertebrae (L2-L4) that were not fractured and not affected by an osteoarthritic process or nonremovable artifacts to such a degree that accurate measurement of BMD would be considered jeopardized by the central reading center.

### *Sample size*

For 90% power and testing superiority hypothesis at  $\alpha = 5\%$ , a sample size of 110 subjects was required (55 subjects per treatment group) for this study. To allow for a 20% drop-out, a total number of 132 subjects (66 per group) were to be randomized.

Subjects were stratified by time since menopause.

Sample size was calculated based on the results from the Phase III oral IBN prevention trial, MF4499, where the strata were 1-3 years and >3 years post menopause (it was assumed that the clinically relevant difference is the same for 0.5-3 years and 1-3 year strata.)

Stratum A (time since menopause: 0.5-3 years): A clinically relevant difference in BMD between IBN monthly and placebo was 2.33%, with a standard deviation of 2.96%;

Stratum B (time since menopause: >3 years): A clinically relevant difference in BMD between IBN monthly and placebo was 3.06%, with a standard deviation of 2.89%.

## **Results**

### *Demographics*

Patients ranged in age from 46 to 60 years of age at baseline. Approximately 95% of the study population was white. Baseline demographics were similar between the treatment groups.

### *Patient Disposition and Analysis Populations*

Eighty-three subjects were randomized to the placebo treatment and 77 to IBN 150mg/month, for a total of 160 subjects. All of these 160 women received at least one dose of study drug and had at least one follow-up assessment. They constitute the safety population as well as the ITT population. Of these, 10 (12%) of the placebo and 12 (16%) of the IBN groups withdrew from treatment before the end of 12 months. Reasons are given in Table 1. Moreover, n=70 women in the placebo and n=68 women had at least one follow-up assessment and were included in the primary analysis population. The per-protocol population consisted of 63 and 58 women in the placebo and IBN groups, respectively.

Table 1. Reasons for withdrawal from treatment.

	Placebo	IBN
AE	3	7
Refused treatment	5	3
Failure to return	1	1
Other	1	1
Total	10	12

### ***Efficacy***

Patients were included in the ITT analysis if they were randomized, received at least one dose of the trial medication and have baseline and at least one follow-up efficacy (sCTX or BMD) data point. This analysis was performed on an ‘as randomized’ basis, i.e., patients who receive medication other than intended were analyzed according to the group to which they were randomized. For the purpose of the statistical analyses the ITT population is the primary population, with 87% of the ITT population contributing information to the primary analysis.

The primary analysis was an ANOVA, including treatment group, time since menopause (as a binary variable, defined as per the randomization strata: 0.5-3.0 years; >3.0 years) and baseline BMD (L2-L4) T-score value as independent variables. Although, as the applicant notes, the protocol does not stipulate the inclusion of baseline BMD (L2-L4) T-score, this factor was included. (I could not find a statistical analysis plan submitted prior to the breaking of the blind.)

Any patients with a time since menopause of < 0.5 years (thereby not fitting into either randomization stratum), was included in the ‘0.5-3.0 years’ category for this analysis.

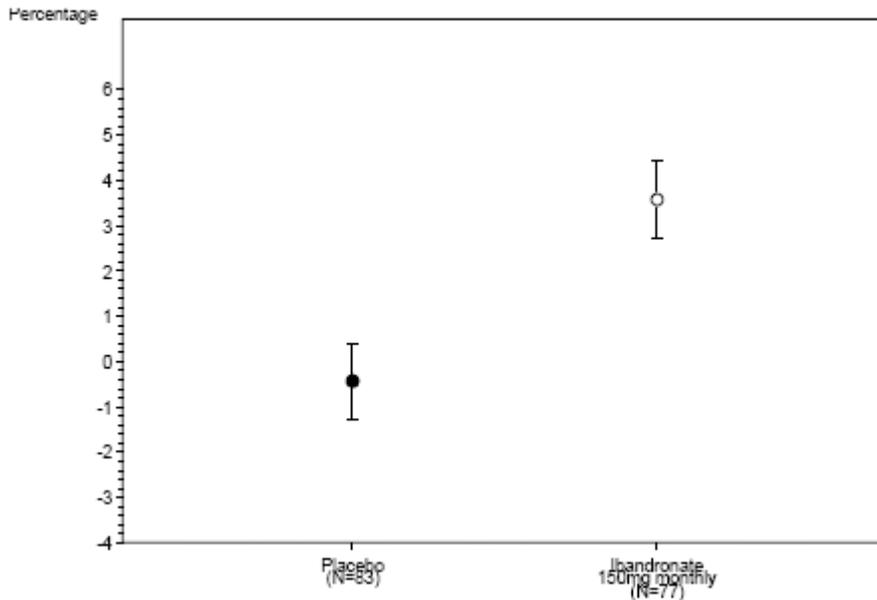
Results of the primary analysis, on the relative change from baseline at month 12 for the lumbar BMD, are given below, in Table 2. The figure below shows graphically the mean relative change from baseline and 95% confidence intervals in the placebo and IBN groups.

The raw mean relative change from baseline to month 12 in lumbar BMD was -0.4 in the placebo group and 3.6 in the ibandronate group. There is a statistically significant difference, in favor of ibandronate, in relative change from baseline in the mean BMD of the lumbar spine at 12 months.

Table 2 Relative Change from Baseline at Month 12, lumbar BMD

	Placebo (n=83)	IBN 150mg (n=77)
N with data	70 (86%)	68 (88%)
Raw mean (S.D.)	-0.43 (3.49)	3.58 (3.48)
Adjusted mean	-0.39	3.73
S.E.	0.41	0.42
Treatment effect	--	4.12
95% CI		2.96, 5.28
P-value		<0.0001

Figure: Mean relative change from baseline and 95% confidence intervals, lumbar spine BMD, in the placebo and IBN groups.



### Other analyses

I repeated the primary analysis with a modified ANOVA model fit, omitting the baseline BMD as a factor to match the plan given in the protocol. The results are nearly identical to those adjusted for baseline BMD; the effect of treatment with IBN is still highly significant and the effect size is similar.

There were a substantial number of patients that did not have month 12 information and were not included in any way in the final analysis: 16% (n=13) in the placebo group and 12% (n=9) in the IBN group. Considering a worse-case scenario, for all dropouts in the IBN group I assumed a change in lumbar spine BMD from baseline at 12 months value equal to the observed mean of the placebo. Similarly, for all dropouts in the placebo group I assumed a change in lumbar spine BMD from baseline at 12 months value equal to the observed mean of the IBN. The resulting means were 3.1 in the IBN group and 0.2 in the placebo, still a large difference.

This sensitivity analysis of the primary endpoint, as well as those conducted by the applicant and the analysis of the secondary endpoints, support the conclusions of the primary analysis of efficacy with differences found in favor of IBN.

## ***Safety***

According to the medical officer's review, among 77 subjects who received ibandronate, safety analysis showed associations between drug intake and adverse gastrointestinal effects and muscle pain. The data support upgrading existing warnings: Current labeling describes the associations as derived from postmarketing reports, implying a frequency lower than detectable in clinical trials.

For more details, see the medical officer's review.

## **Analysis of Subgroups**

*Age, Race, Gender:* All subjects were women between the ages of 46 and 60; most (95%) were white. Therefore, analysis by age, race and gender was not conducted.

*Time since menopause:* IBN had a statistically significant, favorable effect on lumbar spine BMD relative to placebo in both strata defined by time since menopause. The results are shown in table 3a and b, below. The effect was slightly larger in the subjects with >3.0 years since menopause.

Table 3a. Relative Change from Baseline at Month 12, lumbar BMD. Subjects 0.5-3.0 Years since Menopause.

	Placebo (n=49)	IBN 150mg (n=49)
N with data	41	42
Adjusted mean	-0.82	3.15
S.E.	0.56	0.56
Treatment effect	--	3.98
95% CI		2.39, 5.57
P-value		<0.0001

Table 3b. Relative Change from Baseline at Month 12, lumbar BMD. Subjects >3.0 Years since Menopause.

	Placebo (n=34)	IBN 150mg (n=28)
N with data	29	26
Adjusted mean	-0.08	4.50
S.E.	0.56	0.59
Treatment effect	--	4.58
95% CI		2.96, 6.20
P-value		<0.0001

### Conclusions

There is a statistically significant difference, in favor of IBN, in relative change from baseline in the mean BMD of the lumbar spine at 12 months. Sensitivity analyses of the primary endpoint, as well as analysis of the secondary endpoints, further support the efficacy of IBN 150 mg once monthly in the prevention of bone loss in osteopenic women.

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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NDA: 21-455/ SE1-007	Submission Date(s): January 28, 2008
Brand Name	Boniva®
Generic Name	Ibandronate Sodium
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3 (DCP3)
OND division	Division of Reproductive and Urology Products (DRUP)
Sponsor	Hoffman-La Roche
Relevant IND(s)	50,378
Submission Type	Standard
Formulation; Strength(s)	Tablets; 150 mg
Indication	Prevention of Osteoporosis

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**Background:** Ibandronate Sodium (Boniva) is approved as a 2.5 mg once-daily oral tablet (Original NDA 21-455) for the treatment and prevention of osteoporosis in post-menopausal women. It is also approved as a 150 mg once-monthly oral tablet (NDA 21-455/S-001) and as an intravenous formulation (3 mg every 3 months; NDA 21-858) for the treatment of post-menopausal osteoporosis.

**Introduction:** In this efficacy supplement, the sponsor is seeking approval of the 150 mg once monthly tablet formulation in the 'prevention' of osteoporosis. To support this indication, sponsor has submitted results from a new 'prevention' clinical trial comparing 150 mg ibandronate to placebo in N = 160 osteopenic post-menopausal women, treated for 12 months.

**Clinical Pharmacology summary:** No new Clinical Pharmacology information has been submitted with this efficacy supplement. The new prevention clinical trial employed the approved 150 mg ibandronate tablet formulation. The pharmacokinetics of Ibandronate following the 150 mg tablet as well as the drug interaction and special population dosing issues for Ibandronate were found to be adequately addressed during the previous NDA reviews. There were no pending Clinical Pharmacology issues from the three earlier approvals.

**Recommendation:** The NDA is acceptable from a Clinical Pharmacology perspective provided an agreement can be reached with the sponsor regarding the labeling language.

Labeling Review: The revised labeling has been submitted in the new PLR format.

The following revisions to the label are recommended by the Office of Clinical Pharmacology:

## **2 DOSAGE AND ADMINISTRATION**

Change From:



Change To:

### **2.5 Use in Specific Populations**

**BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance of <30 mL/min) [REDACTED].**

**No dose adjustment is necessary for patients with mild or moderate renal impairment. No dose adjustments are necessary for the elderly, or for patients with hepatic impairment.**

## **5 WARNINGS AND PRECAUTIONS**

Add:

### **5.5 Severe Renal Impairment**

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

## **7 DRUG INTERACTIONS**

Add:

### **7.3 H2 Blockers**

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

### **12.3 Pharmacokinetics**



Change To: Specific Populations

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Sandhya Apparaju  
7/16/2008 11:11:21 AM  
BIOPHARMACEUTICS

Myong-Jin Kim  
7/16/2008 02:22:28 PM  
BIOPHARMACEUTICS

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 21455 Supplement 007

**NDA/BLA Number:** 21-455/S-007      **Applicant:** Roche Pharmaceuticals      **Stamp Date:** 01/28/2008

**Drug Name:** Ibandronate      **NDA/BLA Type:** Efficacy  
**Sodium (Boniva)**      **Supplement**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
<b>Criteria for Refusal to File (RTF)</b>				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X	<i>Not applicable</i> as the clinical trial employed a currently approved formulation (150 mg tablets)
2	Has the applicant provided metabolism and drug-drug interaction information?	X		Ibandronate is an approved drug; Drug interactions and metabolism issues were found to be adequately addressed during the approval of original NDA review.
<b>Criteria for Assessing Quality of an NDA</b>				
<b>Data</b>				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X	<i>Not applicable</i> ; No new Clinical Pharmacology/ Biopharmaceutics information/datasets are needed for this efficacy supplement
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			<i>Not applicable</i>
<b>Studies and Analyses</b>				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X	<i>Not applicable</i> ; Only one dose was evaluated in this osteoporosis 'prevention' trial, based on prior discussions with DMEP in this regard. The same dose (150 mg once monthly) is also currently approved for the 'treatment' indication.
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X		Protocol for this study including dose selection and control groups were discussed and agreed upon with DMEP
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response		X	<i>Not applicable</i> ; only one dose was evaluated and study did not include any PK

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR NDA 21455 Supplement 007**

	guidance?			assessments.
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		<i>Not applicable</i> for this supplemental NDA as dosing in special populations was adequately addressed and labeled during the original NDA submissions for the once daily and once-monthly regimens of Ibandronate.
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			<i>Not applicable</i> due to the nature of indication (prevention of osteoporosis in post-menopausal women)
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			<i>Not applicable</i>
11	Is the appropriate pharmacokinetic information submitted?	X		PK information for the 150 mg tablet was included in supplement # 001 and found acceptable (approved March, 2005)
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		Original NDA information
<b>General</b>				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?			<i>Not applicable</i> as no new Clinical Pharmacology/ Biopharmaceutics information was submitted with this supplement
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?			<i>Not applicable</i>
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?			<i>Not applicable</i>
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			<i>Not applicable</i>
17	Was the translation from another language important or needed for publication?		X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

**Yes.**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 21455 Supplement 007

Potential review issues to be forwarded to the Applicant for the 74-day letter:

**None.**

## Clinical Pharmacology Filing Memo

NDA 21-455/S-007

- Submission Date: January 28, 2008
- Goal Date: November 28, 2008
- Sponsor: Hoffman-La Roche
- Drug: Ibandronate Sodium (Boniva)
- Formulation: 150 mg tablets
- Regimen: Once a month
- Purpose of efficacy supplement: To claim osteoporosis 'prevention' indication for the monthly regimen based on results from a new clinical trial comparing 150 mg ibandronate to placebo in N = 160 post-menopausal women, treated for 12 mo.
- Biopharmaceutics: The clinical trial is said to have employed the 150 mg ibandronate tablet formulation currently approved for once-monthly treatment of osteoporosis.

**Table 1 Lot and Batch Numbers of Study Medication Used**

Film-Coated Tablets	Lot No.	Batch No.
IBN 150 mg	B70773	PT2269C01
IBN Placebo	B70779	PT2266C01

- Pharmacokinetics: The pharmacokinetics of 150 mg once monthly Ibandronate were reviewed with the once-monthly sNDA (#001) and found acceptable.
- Pending Clinical Pharmacology issues: There were no pending clinical pharmacology issues or Phase IV commitments from the previous approval.
- Labeling: Submitted in the new PLR format; No significant changes are made to the content of the clinical pharmacology sections of the labeling. Sponsor has included a new statement in the Pharmacodynamics section communicating the results from serum CTX assay in the new clinical trial patients.

Conclusions: The application is fileable from a Clinical Pharmacology perspective.

Deliverables: Due to the absence of new Clinical Pharmacology information, a detailed review will not be needed for this efficacy supplement. Labeling changes will be

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING CHECKLIST FOR NDA 21455 Supplement 007**

reviewed and a brief memo will be written. A Clinical Pharmacology briefing is not planned.

Sandhya Apparaju, Ph.D.	04/01/2008
Reviewing Pharmacologist	Date

Myong Jin Kim, Pharm.D.	
Team Leader/Supervisor	Date

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Sandhya Apparaju  
4/10/2008 08:08:02 AM  
BIOPHARMACEUTICS

Myong-Jin Kim  
4/10/2008 08:10:40 AM  
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 21455/S-007**

**OTHER REVIEW(S)**

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

## Memorandum

**Date:** September 18, 2008

**To:** Karl Stiller  
Project Manager  
Division of Reproductive and Urologic Products

**From:** Janice Maniwang, Pharm.D., M.B.A.  
Regulatory Review Officer  
Division of Drug Marketing, Advertising and Communications

**Subject:** NDA #21-455  
DDMAC labeling comments for Boniva® (ibandronate sodium)  
tablet draft PI

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### Background

I have considered the current Boniva PI, as well as Fosamax (alendronate sodium), Actonel (risedronate sodium) and alendronate sodium tablets PIs in my review of the Boniva draft PI.

DDMAC appreciates the opportunity to review the proposed product labeling for Boniva, which has been revised to reflect a pending efficacy supplement, and provides the following comments:

### Page 2, Indications and Usage - Prevention of Postmenopausal Osteoporosis



### Page 6 – 7, Gastrointestinal Adverse Events



(b) (4)

Page 10, Pharmacodynamics

(b) (4)

Page 13, Clinical Studies – Daily Dosing

(b) (4)

Page 16, Clinical Studies – Once-Monthly Dosing

(b) (4)

*“BONIVA 150 mg once-monthly resulted in a mean increase in lumbar spine BMD of 4.12% compared with placebo following 1 year of treatment (p<0.0001)...”*

We recommend adding the confidence interval, as stated in the Guidance for Industry for the Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products:

**“Uncertainty of Treatment Effect:** A confidence interval and a p-value provide complementary information, and both should usually be provided when describing uncertainty of the treatment effect. A confidence interval provides a better numerical description of the uncertainty of the treatment

effect and provides some information about its size. A p-value better conveys the strength of the finding (i.e., how likely it is that the observed treatment effect is a chance finding). However, it is generally better not to use a p-value alone.”



Please contact me if you have any questions or comments at (301) 796-3821.

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Janice Maniwang  
9/19/2008 08:51:05 AM  
DDMAC REVIEWER

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 21-455 Supplement # 007 Efficacy Supplement Type SE- 1

Proprietary Name: Boniva  
Established Name: ibandronate sodium  
Strengths: 150 mg

Applicant: Hoffman-La Roche Inc.  
Agent for Applicant (if applicable):

Date of Application: January 25, 2008  
Date of Receipt: January 28, 2008  
Date clock started after UN: January 28, 2008  
Date of Filing Meeting: March 11, 2008  
Filing Date: March 28, 2008  
Action Goal Date (optional):

User Fee Goal Date: 11-28-2008

Indication(s) requested: Treatment and prevention of postmenopausal osteoporosis

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 1  
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain: 5-year, same sponsor

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Description	Paper archive copy volume number	Electronic archive copy folder
1 Table of contents (Index)	n/a	<a href="#">suppltoc.pdf</a>
356h Form	Volume 1	<a href="#">356h.pdf</a>
Cover Letter	Volume 1	<a href="#">cover.pdf</a>

Claim for Categorical Exclusion from Environmental Assessment	n/a	<a href="#">environ.pdf</a>
2 Labeling	n/a	<a href="#">labeling</a>
3 Summary	n/a	<a href="#">summary</a>
8 Clinical	n/a	<a href="#">clinstat</a>
11 Case report tabulations	n/a	<a href="#">crt</a>
12 Case report forms	n/a	<a href="#">crf</a>
13 Patent information	Volume 1	<a href="#">other</a>
14 Patent certification	Volume 1	<a href="#">other</a>
15 Establishment Description	n/a	<a href="#">estab</a>
16 Debarment certification	n/a	<a href="#">other</a>
18 User fee cover sheet	Volume 1	<a href="#">other</a>
19 Financial information	Volume 1	<a href="#">Other</a>
20 Other	Volume 1	<a href="#">other</a>

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge . . . .”*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
**NOTE:** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND 46,266 IND 50,378 IND 59,165 IND 59,166
- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
\*No change to previously approved PPI N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: April 9, 2008

NDA #: 21-455

DRUG NAMES: Boniva (ibandronate sodium)

APPLICANT: Hoffman-La Roche Inc.

**BACKGROUND:**

Boniva 2.5 mg once-daily was approved on May 16, 2003 for the treatment and prevention of postmenopausal osteoporosis. The drug was not marketed by the firm. On March 24, 2005, a supplement was approved that provided for the treatment of postmenopausal osteoporosis in women with Boniva 150 mg once monthly. The immediate supplement provides for once-monthly prevention of postmenopausal osteoporosis with Boniva (ibandronate sodium) 150 mg Tablets.

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

**Discipline/Organization**

**Reviewer**

Medical:	Leslie Furlong
Secondary Medical:	Lisa Soule
Statistical:	Stella Grosser
Pharmacology:	Lynnda Reid
Statistical Pharmacology:	None
Chemistry:	Sharon Kelly
Environmental Assessment (if needed):	None
Biopharmaceutical:	Sandhya Apparaju
Microbiology, sterility:	None
Microbiology, clinical (for antimicrobial products only):	None
DSI:	None
OPS:	None
Regulatory Project Management:	Karl Stiller
Other Consults: DDMAC	Rob Dean

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain: No issues identified to prompt an inspection.
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

- GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

- Establishment(s) ready for inspection? YES  NO
- Sterile product? YES  NO
- If yes, was microbiology consulted for validation of sterilization? YES  NO

ELECTRONIC SUBMISSION:  
Any comments: None

**REGULATORY CONCLUSIONS/DEFICIENCIES:**  
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

Karl Stiller  
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If “No,” skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES  NO

*If “Yes,” skip to question 7.*

4. Is this application for a recombinant or biologically-derived product? YES  NO

*If “Yes “contact your ODE’s Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

*If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

*If “Yes,” to (c), proceed to question 7.*

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

*If “No,” skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is YES  NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Karl Stiller  
4/28/2008 03:18:41 PM  
CSO

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21455/S-007**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-455

SUPPL # 007

HFD # 580

Trade Name Boniva

Generic Name ibandronate sodium

Applicant Name Hoffman La Roche Inc.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study BA18492

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study BA18492

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 50,378      YES       !  
!      ! NO   
! Explain:

Investigation #2  
IND #      YES       !  
!      ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES       !  
!      ! NO   
Explain:      ! Explain:

Investigation #2

!

YES

!

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Karl Stiller  
Title: Regulatory Project Manager  
Date: October 24, 2008

Name of Office/Division Director signing form: Dr. Scott Monroe  
Title: Division Director, Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Scott Monroe  
11/28/2008 10:40:08 AM

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: (b) (4)

Supplement Number: 007

NDA Supplement Type (e.g. SE5): SE1

Division Name: DRUP

PDUFA Goal Date: 11-28-2008

Stamp Date: 1-28-2008

Proprietary Name: Boniva

Established/Generic Name: ibandronate sodium

Dosage Form: tablet

Applicant/Sponsor: Hoffman-LaRoche

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) treatment of postmenopausal osteoporosis

(2) \_\_\_\_\_

(3) \_\_\_\_\_

(4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** prevention of postmenopausal osteoporosis

**Q1:** Is this application in response to a PREA PMC/PMR? Yes  Continue

No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMC/PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMC/PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

			Reason (see below for further detail):			
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

- Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

NDA# **Error! Reference source not found.****Error! Reference source not found.****Error! Reference source not found.** Page 6

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

Karl Stiller  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Karl Stiller

9/2/2008 11:07:08 AM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-455 Supplement Type (e.g. SE5): SE1 Supplement Number: 007

Stamp Date: 1-28-08 PDUFA Goal Date: 11-28-08

HFD 580 Trade and generic names/dosage form: Boniva (ibandronate sodium) tablets

Applicant: Hoffman-LaRoche Therapeutic Class: bisphosphonate

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.  
 No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): treatment of postmenopausal osteoporosis

Each indication covered by current application under review must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: prevention of postmenopausal osteoporosis

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.  
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.  
 No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population  
 Disease/condition does not exist in children  
 Too few children with disease to study  
 There are safety concerns  
 Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

NDA 21-455

Page 3

**This page was completed by:**

*{See appended electronic signature page}*

---

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: \_\_\_Partial Waiver \_\_\_Deferred \_\_\_Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 10/10/2006)

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Karl Stiller

4/23/2008 03:15:06 PM

**BONIVA®** (ibandronate sodium)  
150mg Monthly/Prevention of PMO



**DEBARMENT CERTIFICATION**

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in cursive script that reads "Maria Smith".

10/24/08

Maria Smith, Vice President, Global Head Pharma Development Operations Affiliates

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 21-455 BLA #	NDA Supplement # 007 BLA STN #	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: Boniva Established/Proper Name: ibandronate sodium Dosage Form: tablet		Applicant: Hoffman La Roche, Inc. Agent for Applicant (if applicable):
RPM: Karl Stiller		Division: Division of Reproductive and Urologic Products
<p><b>NDAs:</b>            NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)            Efficacy Supplement:    <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u>            Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated            Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		November 28, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		Approval action taken 3-24-2005
❖ Promotional Materials ( <i>accelerated approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/cder/guidance/2197dft.pdf">www.fda.gov/cder/guidance/2197dft.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application <sup>2</sup> Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC  Comments: _____	
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: _____	10-8-2008
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

<p>• Exclusivity</p>	
<p>• Is approval of this application blocked by any type of exclusivity?</p>	<p><input checked="" type="checkbox"/> No      <input type="checkbox"/> Yes</p>
<p>• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</p>	<p><input checked="" type="checkbox"/> No      <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:</p>
<p>• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</p>	<p><input type="checkbox"/> No      <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:</p>
<p>• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</p>	<p><input type="checkbox"/> No      <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:</p>
<p>• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</p>	<p><input type="checkbox"/> No      <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:</p>
<p>• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</p>	<p><input checked="" type="checkbox"/> No      <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:</p>
<p>❖ Patent Information (NDAs only)</p>	
<p>• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</p>	<p><input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<p>• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</p>	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii)    <input type="checkbox"/> (iii)</p>
<p>• [505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</p>	<p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<p>• [505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p>

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	11-14-2008
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**Officer/Employee List**

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	AP S-007 11-28-2008 AP S-001 3-24-2005
---	---

**Labeling**

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	Included in AP letter
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	1-25-2008
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	NDA 21-858/S-001 8-7-2006 NDA 21-823/S-004 8-17-2006 NDA 20-560/S-052 10-8-2008 NDA 21-575/S-013 10-8-2008 NDA 21-762/S-006 10-8-2008
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 9/5/08

	<input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	11-21-2008 (stamp date)
❖ Labeling reviews (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> RPM N/A <input type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 9-18-2008 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Review(s) (indicate date(s))</li> <li>• Acceptability/non-acceptability letter(s) (indicate date(s))</li> </ul>	N/A

**Administrative / Regulatory Documents**

❖ Administrative Reviews (e.g., RPM Filing Review <sup>4</sup> /Memo of Filing Meeting) (indicate date of each review)	PM/4-28-2008 MO/3-12-2008 PharmTox/3-13-2008 Micro/5-30-2008 – NAI ClinPharm/4-10-2008
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">www.fda.gov/ora/compliance_ref/aip_page.html</a>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP           <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (indicate date)</li> <li>○ If yes, OC clearance for approval (indicate date of clearance communication)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing communications (if located elsewhere in package, state where located)</li> <li>• Incoming submissions/communications</li> </ul>	

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.  
Version: 9/5/08

Postmarketing Commitment (PMC) Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>	
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	Supp Ack Letter 3-5-2008 IR Letter 3-14-2008 IR Letter 4-7-2008
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>PeRC (<i>indicate date; approvals only</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>48-hour alert or minutes, if available</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11-28-2008
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11-25-2008
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	11-13-2008
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None N/A
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	11-13-2008
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	11-13-2008
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Risk Management	
<ul style="list-style-type: none"> <li>Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>REMS Memo (<i>indicate date</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> </ul>	

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 9/5/08

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None N/A
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None N/A
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	7-16-2008
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 10-15-2008
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	10-23-2008
• BLAs only: Facility information review(s) (indicate dates)	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	

<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	
<input checked="" type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	Included in CMC Review 10-23-2008
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs: <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

**Stiller, Karl**

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**From:** Greeley, George  
**Sent:** Wednesday, October 08, 2008 1:05 PM  
**To:** Stiller, Karl  
**Cc:** Addy, Rosemary; Mathis, Lisa  
**Subject:** 10/08/08 PeRC PREA Subcommittee Meeting

**Importance:** High

Karl,

Your product, (b) (4) Boniva, was reviewed by members of the PeRC today and they agreed with the Division's decision to grant a full waiver for this product.

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
Office of New Drugs  
FDA/CDER  
10903 New Hampshire Ave.  
Bldg #22, Room 6467  
Silver Spring, MD 20993-0002  
301.796.4025

 Please consider the environment before printing this e-mail.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. This drug is used to treat and prevent osteoporosis in postmenopausal women.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-455

Hoffman-La Roche, Inc.  
Attention: Ruben Diaz  
Senior Program Manager  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Mr. Diaz:

Please refer to your supplemental new drug application (NDA) dated January 25, 2008, received January 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Boniva (ibandronate sodium) tablets, 150 mg.

We also refer to your submission dated March 27, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on March 28, 2008, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph., M.P.A.  
Chief, Project Management Staff  
Division of Reproduction and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Margaret Kober  
4/7/2008 02:52:08 PM  
Chief, Project Management Staff



NDA 21-455/S-007

**INFORMATION REQUEST LETTER**

Hoffman-La Roche, Inc.  
Attention: Ruben Diaz  
Senior Program Manager  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Mr. Diaz:

Please refer to your January 25, 2008 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Boniva (ibandronate sodium) tablets, 150 mg.

We are reviewing your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1 ) Were any vertebral fractures detected on treatment (treatment-emergent, clinical and nonclinical vertebral fractures)? If so, provide a line listing by treatment group.
- 2 ) Did Subject 67179/1244 have ulcer disease on treatment? How was the diagnosis of H. pylori made? What were her symptoms? The term "Helicobacter pylori" and the therapy she received suggest ulcer disease. Please review source records if necessary.

If you have any questions, call Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph., M.P.A.  
Chief, Project Management Staff  
Division of Reproduction and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Margaret Kober  
4/7/2008 11:53:41 AM  
Chief, Project Management Staff



NDA 21-455\S-007

**INFORMATION REQUEST LETTER**

Hoffman-La Roche, Inc.  
Attention: Ruben Diaz  
Senior Program Manager  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Mr. Diaz:

Please refer to your January 25, 2008 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Boniva (ibandronate sodium) tablets, 150 mg.

We are reviewing your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a line listing of all subjects who received treatment with either placebo or ibandronate but were not included in the primary ITT analysis of BMD at lumbar spine with reason why each subject was not included in the primary ITT analysis.
2. Provide the case report form for subject 67179/1244, and a narrative related to her diagnosis of "H pylori."
3. Submit amended datasets, as follows:
  - a) Add a column providing treatment group (name of trial medication) to the adverse event dataset and any other dataset in the submission that does not have one.
  - b) Add a column providing unique subject identifier (USUBJID) to any dataset in the submission that does not have one.

If you have any questions, call Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph., M.P.A.  
Chief, Project Management Staff  
Division of Reproductive and Urologic Products  
Office of New Drugs  
Center for Drug Evaluation and Research

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Margaret Kober  
3/14/2008 08:59:25 AM  
Chief, Project Management Staff



NDA 21-455/S-007

**PRIOR APPROVAL SUPPLEMENT**

Hoffmann La Roche Incorporated  
Attention: Ruben Diaz  
Senior Program Manager  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Mr. Diaz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Boniva (ibandronate sodium) tablets, 150 mg

NDA Number: 21-455

Supplement number: 007

Review Priority Classification: Standard

Date of supplement: January 25, 2008

Date of receipt: January 28, 2008

This prior approval supplement provides for revisions to the prescribing information to include the additional indication for use of Boniva (ibandronate sodium) tablets, 150 mg, for the prevention of osteoporosis in postmenopausal women.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 28, 2008, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 28, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have requested a waiver from this requirement for this indication. We will inform you of our decision regarding this request in a subsequent communication.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any question, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph., M.P.A.  
Chief, Project Management Staff  
Division of Reproduction and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Margaret Kober  
3/5/2008 08:51:48 AM  
Chief, Project Management Staff

## REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising and Communications (DDMAC) HFD-42, Room 17B-17**  
Attn: Rob Dean

FROM (Name, Office/Division, and Phone Number of Requestor): **Karl Stiller,**  
**Project Manager, Division of Reproductive and Urologic**  
**Drug Products, HFD-580**  
301-796-1993

DATE  
March 3, 2008

IND NO.

NDA NO.  
21-455

TYPE OF DOCUMENT  
**PRIOR APPROVAL**  
**EFFICACY**  
**SUPLEMENT**

DATE OF DOCUMENT  
January 28, 2008

NAME OF DRUG  
**Boniva (ibandronate sodium)**

PRIORITY CONSIDERATION  
**Standard**

CLASSIFICATION OF DRUG  
**Bone/Ca-P metabolism**

DESIRED COMPLETION DATE  
**April 28, 2008**

NAME OF FIRM: **ROCHE**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** This is a request to review the PI for NDA 21-455 S-007. This is an electronic submission that can be found on \\CDSESUB1\NONECTD\N21455\S\_007\2008-01-25 or in EDR.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

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Karl Stiller

3/3/2008 02:39:49 PM