Bonova® 150 mg

RADIANT PHARMACEUTICALS

film-coated tablets

Ibandronic acid INN

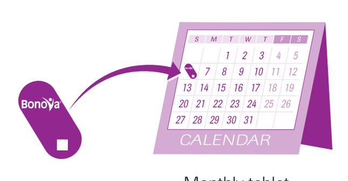
PLANNING WHEN TO TAKE Bonova

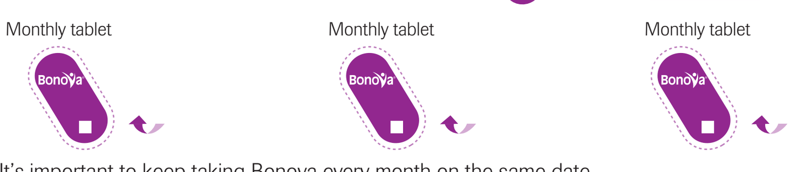
The dose of Bonova is one tablet once a month.
Choose one day of the month that will be easy to remember:

- either the same date (such as the 1st of each month).
- or the same day (such as the first sunday of each month).

Use the peel-off stickers below to mark the dates on your calendar.
Once you've taken your tablet, put a tick in the box on the sticker.

PEEL-OFF STICKERS FOR YOUR CALENDAR
আপনার ক্যালেন্ডারের জন্য পিল-অফ স্টিকার





It's important to keep taking Bonova every month on the same date
প্রতি মাসের একই দিনে বনোভা সেবন করা গুরুত্বপূর্ণ

Bonova® 150 mg

film-coated tablets

Ibandronic acid INN

Bisphosphonate – Drugs for treatment of bone diseases (M05)

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Bonova is a nitrogen-containing bisphosphonate.

1.2 Type of Dosage Form

Film-coated tablets.

1.3 Route of Administration

Oral.

1.4 Qualitative and Quantitative Composition

Active ingredient: Ibandronic acid, monosodium salt, monohydrate

One 150 mg film-coated tablet contains 168.75mg ibandronic acid, monosodium salt, monohydrate equivalent to 150 mg of ibandronic acid.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Bonova 150 mg is indicated for the treatment of postmenopausal osteoporosis, to reduce the risk of fractures.

Treatment of Osteoporosis: Osteoporosis may be confirmed by the finding of low bone mass (T-score <-2.0 SD) and the presence or history of osteoporotic fracture, or a low bone mass (T-score < -2.5 SD) in the absence of documented pre-existing osteoporotic fracture.

2.2 Dosage and Administration

The recommended dose of Bonova for treatment is one 150 mg film-coated tablet once a month. The tablet should preferably be taken on the same date each month. Bonova should be taken 60 minutes before the first food or

drink (other than water) of the day (see section 2.4.3 Interactions with other Medicinal Products and other Forms of Interaction, Drug-Food Interactions) or any other oral medication or supplementation (including calcium):

- Tablets should be swallowed whole with a full glass of plain water (180 to 240 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 60 minutes after taking Bonova.
- Plain water is the only drink that should be taken with Bonova. Please 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.

Patients should receive supplemental calcium or vitamin D if dietary intake is inadequate.
In case a once-monthly dose is missed, patients should be instructed to take one Bonova 150 mg tablet the morning after the tablet is remembered, unless the time to the next scheduled dose is within 7 days. Patients should then return to taking their dose once a month on their originally scheduled date.
If the next scheduled dose is within 7 days, patients should wait until their next dose and then continue taking one tablet once a month as originally scheduled. Patients should not take two 150 mg tablets within the same week.

2.2.1 Special Dosage Instructions

Patients with hepatic impairment
No dosage adjustment is necessary (see section 3.2.5 Pharmacokinetics in Special Populations).
Patients with renal impairment
No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is ≥ 30 mi/mm.
Below 30 ml/mm creatinine clearance, the decision to administer Bonova should be based on an individual risk-benefit assessment (see section 3.2.5 Pharmacokinetics in Special Populations).

Elderly
No dosage adjustment is necessary.

Children
Safety and efficacy have not been established in patients less than 18 years old.

2.3 Contraindications

Bonova is contraindicated in patients with known hypersensitivity to ibandronic acid or to any of the excipients. Bonova is contraindicated in patients with uncorrected hypocalcemia. As with all bisphosphonates indicated in the treatment of osteoporosis, pre-existing hypocalcemia needs to be corrected before initiating therapy with Bonova. As with several bisphosphonates, Bonova is contraindicated in patients with abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia (see section 2.4 Warnings and Precautions). Bonova is contraindicated in patients who are unable to stand or sit upright for at least 60 minutes (see sections 2.2 Dosage and Administration and 2.4 Warnings and Precautions).

2.4 Warnings and Precautions

2.4.1 General

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Bonova therapy. Adequate intake of calcium and vitamin D is important in all patients.
Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Bonova is given to patients with active upper gastrointestinal problems (e.g. known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers). Adverse experiences such as esophagitis, esophageal ulcers and esophageal erosions, in some cases severe and requiring hospitalization, rarely with bleeding or followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. The risk of severe esophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Patients should pay particular attention and be able to comply with the dosing instructions (see section 2.2 Dosage and Administration).

Physicians should be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue Bonova and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.
While no increased risk was observed in controlled clinical trials there have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications. Since NSAIDs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant medication with Bonova.
Osteonecrosis of the jaw (ONJ) 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 of the jaw 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. For patients who develop

osteonecrosis of the jaw 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.

2.4.2 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

2.4.3 Interactions with other Medicinal Products and other Forms of Interaction

Drug-Food Interactions
Products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk and food, are likely to interfere with absorption of Bonova which is consistent with findings in animal studies. Therefore, with such products, including food, intake must be delayed for 60 minutes following oral administration.

Drug-Drug Interactions
It is likely that calcium supplements, antacids and some oral medications containing multivalent cations (such as aluminium, magnesium, iron) are likely to interfere with the absorption of Bonova. Therefore, patients must wait 60 minutes after taking Bonova before taking other oral medications. Pharmacokinetic interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (estrogen). No interaction was observed when co-administered with melphalan/prednisolone in patients with multiple myeloma. In healthy male volunteers and postmenopausal women, i.v. ranitidine caused an increase in ibandronic acid bioavailability of about 20 %, probably as a result of reduced gastric acidity. However, since this increase is within the normal range of the bioavailability of ibandronic acid, no dosage adjustment is required when Bonova is administered with H_2-antagonists or other drugs which increase gastric pH.
In relation to disposition, no drug interactions of clinical significance are considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats. Furthermore, plasma protein binding is low at therapeutic concentrations and

ibandronic acid is therefore unlikely to displace other drugs. Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation. The secretory pathway appears not to include known acidic or basic transport systems involved in the excretion of other drugs.

In a one-year study in postmenopausal women with osteoporosis (BM16549). the incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking Bonova 2.5mg daily or 150mg once monthly. Of over 1500 patients enrolled in study BM 16549 comparing monthly with daily dosing regimens of ibandronic acid, 14% of patients used histamine (H_2) blockers or proton pump inhibitors. Among these patients, the incidence of upper gastrointestinal events in the patients treated with Bonova 150 mg once monthly was similar to that in patients treated with Bonova 2.5 mg daily.

2.5 Use in Special Populations

2.5.1 Pregnancy

Bonova should not be used during pregnancy.

There was no evidence for a direct fetal toxic or teratogenic effect of ibandronic acid in daily orally treated rats and rabbits and there were no adverse effects on the development in F1 offspring in rats. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those observed with bisphosphonates as a class. They include a decreased number of implantation sites, interference with natural delivery (dystocia), and an increase in visceral variations (renal pelvis ureter syndrome). Specific studies for the monthly regimen have not been performed. There is no clinical experience with Bonova in pregnant women.

2.5.2 Nursing Mothers

Bonova should not be used during lactation.
In lactating rats treated with 0.08 mg/kg/day iv. ibandronic acid, the highest concentration of ibandronic acid in breast milk was 8.1 ng/ml and was seen in the first 2 hours after i.v. administration. After 24 hours, the concentration in milk and plasma was similar, and corresponded to about 5 % of the concentration measured after 2 hours.

It is not known whether Bonova is excreted in human milk.

2.5.3 Pediatric Use

See section 3.2.5 Pharmacokinetics in Special Populations, Children

2.5.4 Geriatric Use

See section 3.2.5 Pharmacokinetics in Special Populations, Elderly

2.5.5 Renal Impairment

See section 3.2.5 Pharmacokinetics in Special Populations, Patients with renal impairment

2.5.6 Hepatic Impairment

See section 3.2.5 Pharmacokinetics in Special Populations, Patients with hepatic impairment.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Treatment of postmenopausal osteoporosis
Once-monthly dosing
In a two-year study in postmenopausal women with osteoporosis (BM 16549) the overall safety of Bonova 150

mg once monthly and Bonova 2.5 mg daily was similar. The overall proportion of patients who experienced an adverse drug reaction, i.e. adverse event with a possible or probable relationship to trial medication, was 22.7 % and 25.0 % for Bonova 150mg once monthly and 21.5 % and 22.5 % for Bonova 2.5 mg daily after one and two years, respectively. The majority of adverse drug reactions were mild to moderate in intensity. Most cases did not lead to cessation of therapy.

Tables 1 and 2 list adverse drug reactions occurring in more than I % of patients treated with Bonova 150 mg monthly or 2.5 mg daily in study BM 16549 and in patients treated with Bonova 2.5 mg daily in study MF 4411. The tables show the adverse drug reactions in the two studies that occurred with a higher incidence than in patients treated with placebo in study MF 4411. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Data at one year from BM 16549 are represented in Table 1 and cumulative data for the two years from BM 16549 are represented in Table 2.

Table 1: Common adverse drug reactions (>1/100, ≤ 1/10) in phase III osteoporosis studies that were considered by the investigator to be possibly or probably related to treatment - One year data from study BM 16549 and three year data from placebo-controlled fracture study MF 4411

	One year data in study BM 16549		Three year data in study MF 4411	
System Organ Class/ Adverse drug reaction	Bonova 150 mg once monthly (N=396) (%)	Bonova 2.5 mg daily (N=395) (%)	Bonova 2.5 mg daily (N = 977) (%)	Placebo (N = 975) (%)
Gastrointestinal system				
Gastro-oesophageal reflux disease	0.5	1.0	0.4	0.1
Diarrhoea	2.5	1.8	1.4	1.0
Abdominal pain	3.5	2.8	2.1	2.9
Dyspepsia	3.3	5.8	4.3	2.9
Nausea	3.3	3.5	1.8	2.3
Flatulence	0.5	1.0	0.4	0.7
Nervous system				
Headache	0.8	1.5	0.8	0.6
General disorders				
Influenza like illness*	3.3	0.3	0.3	0.2
Fatigue	1.0	0.3	0.3	0.4
Musculoskeletal system				
Arthralgia	1.0	0.3	0.4	0.4
Myalgia	1.5	0.3	1.8	0.8
Skin disorders				
Rash	0.8	1.0	1.2	0.7

MedDRA version 6.1

* Transient, influenza-like symptoms have been reported with Bonova 150 mg once monthly, typically in association with the first dose. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures. Influenza-like illness includes events reported as acute phase reaction or symptoms including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, or bone pain.

Table 2: Cumulative common adverse drug reactions (>1/100, ≤ 1/10) in Phase III osteoporosis studies that were considered by the investigator to be possibly or probably related to treatment - Two year data from study BM 16549 and three year data from placebo-controlled fracture study MF 4411

	Two year cumulative data in study BM 16549		Three year data in study MF 4411	
System Organ Class/ Adverse drug reaction	Bonova 150 mg once monthly IN=396) (%)	Bonova 2.5 mg daily (N=395) (%)	Bonova 2.5 mg daily (N = 977) (%)	Placebo (N=977) (%)
Gastrointestinal system				
Gastritis	1.0	0.3	0.7	0.5
Gastro-oesophageal reflux disease	0.8	1.0	0.5	0.1

	Two year cumulative data in study BM 16549		Three year data in study MF 4411	
System Organ Class/ Adverse drug reaction	Bonova 150 mg once monthly (N=396) (%)	Bonova 2.5 mg daily (N=395) (%)	Bonova 2.5 mg daily (N=977) (%)	Placebo (N=975) (%)
Oesophagitis	0	1.0	0.5	0.4
Diarrhoea	2.5	2.0	1.4	1.0
Abdominal pain	4.0	3.0	2.1	2.9
Dyspepsia	4.0	6.3	4.0	2.7
Nausea	3.0	3.5	1.8	2.3
Nervous system				
Headache	0.8	1.5	0.8	0.6
General disorders				
Influenza like illness*	3.3	0.3	0.3	0.2
Musculoskeletal system				
Muscle cramp	0.5	1.0	0.1	0.4
Musculoskeletal pain	1.0	0.5	0	0
Arthralgia	1.0	0.5	0.4	0.4
Myalgia	1.5	0.3	1.8	0.8
Musculoskeletal stiffness	1.0	0	0	0
Skin disorders				
Rash	1.0	0	0	0

MedDRA version 7.1

influenza-like symptoms have been reported with Bonova 150 mg once monthly, typically in association with the first dose. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures. Influenza'like illness includes events reported as acute phase reaction or symptoms including myalgia. arthralgia. fever. chills. fatigue. nausea. loss of apetite. or bone pain.

Adverse drug reactions occurring at a frequency of less than or equal to 1 % The following list provides information on adverse drug reactions (considered possibly or probably related to treatment by the investigator) reported in study MF 4411 occurring more frequently with Bonova 2.5 mg daily than with placebo and study BM 16549 occurring more frequently with Bonova 150 mg once monthly than with Bonova 2.5 mg daily. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:
Uncommon (1/100 – 1/1,000)
Gastrointestinal Disorders: gastritis, oesophagitis including oesophageal ulcerations or strictures, vomiting, dysphagia
Nervous System Disorders: dizziness
Musculoskeletal and Connective Tissue Disorders: back pain

Rare (1/1,000 – 1/10,000)
Gastrointestinal Disorders: duodenitis
Immune System Disorders: hypersensitivity reactions

Skin and Subcutaneous Tissue Disorders: angioedema, face oedema, urticaria Patients with a previous history of gastrointestinal disease including patients with peptic ulcer without recent bleeding or hospitalisation, and patients with dyspepsia or reflux controlled by medication were included in the once monthly treatment study. For these patients, there was no difference in the incidence of upper gastrointestinal adverse events with the 150 mg once monthly regimen compared to the 2.5 mg daily regimen.

2.6.1.1 Laboratory Abnormalities

In the pivotal three-year study with Bonova 2.5 mg daily (MF 4411) there was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, impaired hematologic system, hypocalcemia or hypophosphatemia. Similarly, no differences were noted between the groups in study BM 16549 after one and two years.

2.6.2 Post Marketing

Musculoskeletal and connective tissue disorders:

Osteonecrosis of the jaw has been reported very rarely in patients treated with ibandronic acid (refer to 2.4 Warnings and Precautions).
Eye disorders:

Ocular inflammation events such as uveitis, episcleritis and scleritis have been reported with bisphosphonates, including ibandronic acid. In some cases, these events did not resolve until the bisphosphonate was discontinued.

2.7 Overdose

No specific information is available on the treatment of overdosage with Bonova. However, oral overdosage may result in upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer. Milk or antacids should be given to bind Bonova. Owing to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

The pharmacodynamic action of ibandronic acid is inhibition of bone resorption. In vivo, ibandronic acid prevents experimentally induced bone destruction caused by cessation of gonadal function, retinoids, tumors or tumor extracts. In young (fast growing) rats, the endogenous bone resorption is also inhibited, leading to increased bone mass compared with untreated animals. Animal models confirm that ibandronic acid is a highly potent inhibitor of osteoclastic activity. In growing rats, there was no evidence of impaired mineralization even at doses greater than 5,000 times the dose required for osteoporosis treatment. The high potency and therapeutic margin of ibandronic acid allows for more flexible dosing regimens and intermittent treatment with long drug-free intervals at comparatively low doses.

Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys were associated with formation of new bone of normal quality and/or increased mechanical strength even in doses in excess of any pharmacologically intended dose, including the toxic range. In humans, the efficacy

of both daily and intermittent administration with a dose-free interval of 9-10 weeks of ibandronic acid was confirmed in a clinical trial (MF 4411), in which Bonova demonstrated anti-fracture efficacy.

Both daily and intermittent (with a drug-free interval of 9-10 weeks per quarter) oral doses of Bonova in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including suppression of urinary biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked C- and N-telopeptides of type I collagen).

Following treatment discontinuation, there is a reversion to the pathological pre-treatment rates of elevated bone resorption associated with postmenopausal osteoporosis.
The histological analysis of bone biopsies after two and three years of treatment of postmenopausal women showed bone of normal quality and no indication of a mineralization defect.
In a Phase 1 bioequivalence study conducted in 72 postmenopausal women receiving 150 mg orally every 28 days for a total of four doses, inhibition in serum CTX following the first dose was seen as early as 24 hours

post-dose (median inhibition 28%), with median maximal inhibition (69%) seen 6 days later. Following the third and fourth dose, the median maximum inhibition 6 days post dose was 74% with reduction to a median inhibition of 56% seen 28 days following the fourth dose. With no further dosing, there is a loss of suppression of biochemical markers of bone resorption.

3.1.1 Mechanism of Action

Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act on bone tissue and specifically inhibit osteoclast activity, It does not interfere with osteoclast recruitment. The selective action of ibandronic acid on bone tissue is based on the high affinity of this compound for hydroxyapatite, which represents the mineral matrix of the bone. Ibandronic acid reduces bone resorption, with no direct effect on bone formation. In postmenopausal women, it reduces the elevated rate of bone turnover towards premenopausal levels, leading to a progressive net gain in bone mass. Daily or intermittent administration of ibandronic acid results in reduced bone resorption as reflected in reduced levels of serum and urinary biochemical markers of bone turnover, increased BMD and a decreased incidence of fractures.

3.1.2 Clinical / Efficacy Studies

Treatment of postmenopausal osteoporosis
In the initial three-year, randomized, double-blind, placebo-controlled, fracture study (MF 4411). a statistically significant and medically relevant decrease in the incidence of new radiographic morphometric and clinical vertebral fractures was demonstrated. Bonova was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently (20 mg every other day for 12 doses at the start of each 3-month cycle, followed by a 9-10 week drug-free interval). Bonova was taken 60 minutes

before the first food or drink of the day (post-dose fasting period). The study enrolled 2,946 women aged 55 to 80 years (2,928 were eligible for efficacy), who were at least 5 years postmenopausal, who had a lumbar spine BMD 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral fractures. All patients received 500 mg calcium and 400 IU vitamin D daily.
Bonova showed a statistically significant and medically relevant reduction in the incidence of new vertebral fracture with both regimens tested. The 2.5 mg daily regimen reduced the occurrence of new radiographic

vertebral fractures by 62% over the three year duration of the study. Clinical vertebral fractures were also reduced by 49%. The strong effect on vertebral fractures was furthermore reflected by a statistically significant reduction of height loss compared to placebo.

The anti-fracture effect was consistent over the duration of the study. There was no indication of a waning of the effect over time.
Although the clinical fracture trial for ibandronic acid was not specifically designed to demonstrate fracture efficacy in non-vertebral fractures, a relative risk reduction of similar magnitude (69%) as demonstrated for vertebral fractures was observed for non-vertebral fractures in a subgroup of patients being at higher fracture risk (femoral neck BMD T–score <–3.0 SD). The observation of non-vertebral fracture efficacy in high-risk subgroups is consistent with clinical trial findings for other bisphosphonates.

Three-year lumbar spine BMD increase compared to placebo was 5.3% for the daily regimen. Compared to baseline this increase was 6.5%.

Biochemical markers of bone turnover (such as urinary CTX and serum osteocalcin) showed the expected pattern of suppression to premenopausal levels and reached maximum suppression within a period of 3-6 months. A clinically meaningful reduction of 50% and 78 % of biochemical markers of bone resorption was observed as early as one month after start of treatment with Bonova 2.5 mg daily and 20 mg intermittently, respectively. Decreases in biochemical markers of bone resorption were evident within 7 days of starting treatment.
Bonova 150 mg once monthly Bone mineral density
Bonova 150 mg once monthly was shown to be at least as effective as Bonova 2.5mg daily at increasing BMD in a two year, double-blind, multicentre study (BM
16549) of postmenopausal women with osteoporosis (lumbar spine BMD T score below -2.5 SD at baseline). This was demonstrated in both the primary analysis at one year and in the confirmatory analysis at two years endpoint (Table 3).

Table 3: Mean relative change from baseline of lumbar spine, total hip, femoral neck and trochanter BMD after one year (primary analysis) and two years of treatment (Per-Protocol Population) in study BM 16549

	One year data in study BM 16549		Two year data in study BM 16549	
Mean relative changes from baseline % 195% CI]	Bonova 2.5 mg daily (N=318) (%)	Bonova 2.5 mg Once monthly (N=320) (%)	Bonova 2.5 mg Once monthly (N=294) (%)	Bonova 2.5 mg Once monthly (N=291) (%)
Lumbar spine L2-L4 BMD	3.9 [3.4, 4.3]	4.9 [4.4, 5.3]	5.0 [4.4, 5.5]	6.6 [6.0, 7]
Total hip BMD	2.0 [1.7, 2.3]	3.1 [2.8, 3.4]	2.5 [2.1, 2.9]	4.2 [3.8, 4.5]
Femoral neck BMD	1.7 [1.3, 2.1]	2.2 [1.9, 2.6]	1.9 [1.4, 2.4]	3.1 [2.7, 3.6]
Trochanter BMD	3.2 [2.8, 3.7]	4.6 [4.2. 5.1]	4.0 [3.5,.7, 6.7]	6.2 [5.7,6.7]

Furthermore, Bonova 150 mg once monthly was proven superior to Bonova 2.5 mg daily for increases in lumbar spine BMD in a prospectively planned analysis at one year, p=0.002, and at two years, p<0.001.
At one year (primary analysis), 91.3 % (p=0.005) of patients receiving Bonova 150mg once monthly had a lumbar spine BMD increase above or equal to baseline (BMD responders), compared with 84.0 % of patients receiving Bonova 2.5 mg daily. At two years, 93.5 % (p=0.004) and 86.4 % of patients receiving Boneviva 150 mg once monthly or Boneviva 2.5 mg daily, respectively, were responders.
For total hip BMD, 90.0 % (p<0.001) of patients receiving Bonova 150 mg once monthly and 76.7 % of patients receiving Bonova 2.5 mg daily had total hip BMD increases above or equal to baseline at one year. At two years, 93.4 % (p<0.001) of patients receiving Bonova 150 mg once monthly and 78.4 % of patients receiving Bonova 2.5 mg daily had total hip BMD increases above or equal to baseline.

When a more stringent criterion is considered, which combines both lumbar spine and total hip BMD, 83.9 % (p<0.001) and 65.7 % of patients receiving Bonova 150 mg once monthly or Bonova 2.5 mg daily, respectively, were responders at one year. At two years, 87.1 % (p<0.001) and 70.5 %,of patients met this criterion in the 150

mg monthly and 2.5 mg daily arms respectively.
Biochemical markers of bone turn-over
Clinically meaningful reductions in serum CTX levels were observed at all time points measured, i.e. months 3, 6, 12 and 24. After one year (primary analysis) the median relative change from baseline was -76 % for Bonova 150 mg once monthly and -67 % for Bonova 2.5 mg daily. At two years the median relative change was -68 % and -62 %, in the 150 mg monthly and 2.5 mg daily arms respectively.

At one year, 83.5 % (p= 0.006) of patients receiving Bonova 150mg once monthly and 73.9 % of patients receiving Bonova 2.5 mg daily were identified as responders (defined as a decrease ≥50 % from baseline). At two years 78.7 % (p=O.OO2) and 65.6 % of patients were identified as responders in the 150 mg monthly and 2.5 mg daily arms respectively.

Based on the results of study BM 16549, Bonova 150 mg once monthly is expected to be at least as effective in preventing fractures as Bonova 2.5 mg daily.

3.2 Pharmacokinetic Properties

The pharmacological effects of ibandronic acid are not directly related to actual plasma concentrations. This was demonstrated by various studies in animals and in humans, in which equivalent efficacy of ibandronic acid was demonstrated

following either daily or intermittent regimens, consisting of a drug-free interval of several weeks (at least 6 weeks in rats, at least 11 weeks in dogs, at least 30 days in monkeys, and at least 9.5 weeks in humans) provided the same total dose was administered over this period.

3.2.1 Absorption

The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration and plasma concentrations increase in a dose-proportional manner up to 50 mg oral intake, with greater than dose-proportional increases seen above this dose. Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6%. The extent

of absorotion is impaired when taken together with food or beverages (other than plain water). Bioavailability is reduced by about 90% when ibandronic acid is administered with a standard breakfast in comparison with bioavallabiity seen in fasted subjects. There is no meaningful reduction in bioavailabllity provided ibandronic acid is taken 60 minutes before a meal. Both bioavailability and BMD gains are reduced when food or beverage are taken less than 60 minutes after Bonova.

3.2.2 Distribution

After initial systemic exposure, ibandronic acid 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 reaching the bone is estimated to be 40-50% of the circulating dose. Protein binding in human plasma is low (approximately 85% bound at therapeutic concentrations), and thus there is a low potential for drug-drug interaction due to displacement.

3.2.3 Metabolism

There is no evidence that ibandronic acid is metabolized in animals or humans.

3.2.4 Elimination

The absorbed fraction of ibandronic acid is removed from the circulation via bone absorption (40-50%) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid is eliminated unchanged in the feces.
The range of observed apparent half-lives is broad and dependent on dose and assay sensitivity, but the apparent terminal half-life is generally in the range of 10-72 hours. Early plasma levels fall quickly reaching 10% of peak values within
3 and 8 hours after intravenous or oral administration respectively.
Total clearance of ibandronic acid is low with average values in the range 84- 160 ml/mm. Renal clearance (about 60 ml./min in healthy postmenopausal
females) accounts for 50-60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances is considered to reflect the uptake by bone.

3.2.5 Pharmacokinetics in Special Populations

Gender
Bioavailability and pharmacokinetics of ibandronic acid are similar in both men and women.

Race
There is no evidence for clinically relevant interethnic differences between Asians and Caucasians in ibandronic acid disposition. There are few data available on patients of African origin.

Patients with renal impairment
Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLcr).
No dosage adjustment is necessary for patients with mild or moderate renal impairment (CLcr ≥30 mi/mm), as shown in study BM 16549 where the majority of patients fell into these categories.

Subjects with severe renal impairment (CLcr ≤ 30 ml/mm) receiving oral administration of 10 mg ibandronic acid daily for 21 days, had 2-3 fold higher plasma concentrations than subjects with normal renal function (total clearance = 129 ml/mm). Total clearance of ibandronic acid was reduced to 44 ml/mm in the subjects with severe renal impairment. After iv. administration of 0.5 mg, total, renal, and non-renal clearances decreased by 67%, 77% and 50%, respectively, in subjects with severe renal impairment. However, there was no reduction in tolerability associated with the increase in exposure.

Patients with hepatic impairment
There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid.

3.3 Preclinical Safety

Toxic effects in animals were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

3.3.1 Carcinogenicity

No indication of carcinogenic potential has been observed.

3.3.2 Mutagenicity

No indication of genotoxic potential has been observed.

4. PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Tablet core

Microcrystalline Cellulose	Ph. Eur./NF
Colloidal Silicon Dioxide	Ph. Eur./NF
Sodium Starch Glycolate	Ph. Eur./NF
Sodium Stearyl Fumarate	Ph. Eur./NF

Tablet coat

Part Hydrolyzed Polyvinyl Alcohol	Ph. Eur./NF
Titanium Dioxide	Ph. Eur./USP
Talc	Ph. Eur./USP
Macrogol, 3350	Ph. Eur./NF
Lecithin (soya)	Ph. Eur./NF

4.2 Storage

Keep in a cool and dry place. Do not store above 30°C.
Keep out of reach of children.

4.3 Special Instructions for Use, Handling and Disposal

This medicine should not be used after the expiry date (EXP) shown on the pack.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems" if available in your location.

4.4 Packs

Bonova® 150 mg tablet: Each box contains One tablet in blister pack.

Current at July 2012

® Registered Trade Mark

RADIANT PHARMACEUTICALS
Manufactured by
Radiant Pharmaceuticals Limited
at Pharmacil Limited
Tongi, Bangladesh.

Version: 01

PMR5351

বনোভা® ১৫০ মি.গ্রা.

RADIANT PHARMACEUTICALS

ফিল্ম-কোটেড ট্যাবলেট

ইবানড্রোনিক এসিড আইএনএন

বনোভা® ১৫০ মি.গ্রা.

ফিল্ম-কোটেড ট্যাবলেট

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উপাদান ঃ

বনোভা® ১৫০ মি. গ্রা. ট্যাবলেট: প্রতিটি ফিল্ম-কোটেড ট্যাবলেটে রয়েছে ইবানড্রোনেট সোডিয়াম মনোহাইড্রেট আইএনএন যা ১৫০ মি.গ্রা. ইবানড্রোনিক এসিড এর সমতুল্য।

ইবানড্রোনিক এসিড অস্টিওক্লাস্টের কার্যক্রম প্রতিরোধ করে এবং বোন রিসর্পশন ও টার্নওভার হ্রাস করে। এটি মেনোপজ পরবর্তী মহিলাদের বোন টার্নওভার হার কমিয়ে পর্যায়ক্রমে হাড়ের ওজন বৃদ্ধি করে। ইবানড্রোনেট খাদ্যনালীর উর্ধ্বাংশে শোষিত হওয়ার পর হাড়ের সাথে দ্রুত আবদ্ধ হয় অন্যথায় অপরিবর্তিতভাবে মূত্রের সাথে বেরিয়ে যায়।

নির্দেশনা ঃ

বনোভা® মহিলা এবং পুরুষদের অস্টিওপোরোসিস প্রতিরোধে ও চিকিৎসায় নির্দেশিত।

কিডনীর রোগীদের ক্ষেত্রে ঃ

সামান্য থেকে মাঝারি ধরনের কিডনীর সমস্যায় (ক্রিয়েটিনিন ক্লিয়ারেন্স ৩০ মি.লি./মিনিট বা এর বেশী হলে) প্রয়োগমাত্রায় কোন পরিবর্তন করার প্রয়োজন নেই।

বয়স্কদের ক্ষেত্রে ঃ

প্রয়োগমাত্রায় কোন পরিবর্তন করার প্রয়োজন নেই।

প্রয়োগবিধি ঃ

সর্বোচ্চ শোষণ এবং কার্যকারিতার জন্য **বনোভা®** ১৫০ মি.গ্রা. ট্যাবলেট নির্ধারিত দিনে

পার্শ্বপ্রতিক্রিয়া ঃ

বনোভা® এর প্রধান পার্শ্বপ্রতিক্রিয়াগুলো হচ্ছে ডিসপেপ্সিয়া, বমি বমি ভাব, ডায়রিয়া, পেটে ব্যথা, পেশীতে ব্যথা, মাথা ব্যথা, মাথা ঝিমঝিম করা।

প্রতিনির্দেশনা ঃ

ইবানড্রোনিক এসিড বা এর যেকোন উপাদানের প্রতি অতিসংবেদনশীল রোগীদের জন্য **বনোভা®** প্রতিনির্দেশিত।

ড্রাগ ইন্টার‍্যাকশন ঃ

ক্যালসিয়াম ও অন্যান্য মাল্টিভ্যালেন্ট ক্যাটায়ন (অ্যালুমিনিয়াম, ম্যাগনেশিয়াম, আয়রন) ইবানড্রোনেটের শোষণ ব্যাহত করায় **বনোভা®** নেয়ার পর ১ ঘন্টা পরে খাদ্য বা অন্য ওষুধ খেতে হবে।

গর্ভাবস্থায় এবং স্তন্যদানকালে ঃ

গর্ভাবস্থায় এবং স্তন্যদানকালে **বনোভা®** খাওয়া উচিত নয়।

বিস্তারিত তথ্যের জন্য ইংরেজী অংশ পড়ুন।
তথ্য আধুনিকায়ন জুলাই ২০১২

® রেজিস্ট্রার্ড ট্রেডমার্ক

RADIANT PHARMACEUTICALS

প্রস্তুতকারক
রেডিয়েন্ট ফার্মাসিউটিক্যাল্স লিমিটেড
কর্তৃক ফার্মাসিল লিমিটেড-এ প্রস্তুতকৃত
টঙ্গী, বাংলাদেশ।

বনোভা® খাওয়ার দিন নির্ধারণ

বনোভা® ট্যাবলেট মাসে একটি করে খেতে হয়।

- **বনোভা®** খাওয়ার জন্য এমন একটি দিন বেছে নিন যা আপনার জন্য মনে রাখা সুবিধাজনক (যেমন মাসের প্রথম দিন)।
- আপনার পরবর্তী **বনোভা®** ট্যাবলেট খাবার দিনটিকে লিফলেটের সাথে দেয়া পিল-অফ স্টিকার (ইংরেজী অংশের তৃতীয় পৃষ্ঠায় দেয়া আছে) দিয়ে চিহ্নিত করে রাখুন।
- প্রয়োজনে ডাক্তারের পরামর্শ নিন।

বিবরণ ঃ

অস্টিওপোরোসিস একটি রোগ যেটা হাড়কে দুর্বল করে ফেলে। অস্টিওপোরোসিস পুরুষ এবং মহিলা উভয় ক্ষেত্রে হতে পারে তবে মেনোপজ (৪৫-৫০ বছর বেশী বয়স্ক মহিলাদের মাসিক বন্ধ হয়ে যাওয়া) পরবর্তী মহিলাদের বেশী হয়ে থাকে। অস্টিওপোরোসিসে প্রথমদিকে উপসর্গগুলি দেখা দেয় না। তা সত্ত্বেও অস্টিওপোরোসিসের রোগীদের উচ্চতা কিছুটা কমে যেতে পারে এবং তাদের হাড় বিশেষ করে মেরুদন্ড, হাতের কব্জি, হিপ বোন ভেঙ্গে যেতে পারে। অস্টিওপোরোসিস প্রতিরোধ করা যায় এবং সঠিক ওষুধের মাধ্যমে চিকিৎসা করা যায়।

প্রয়োগমাত্রা ঃ

অস্টিওপোরোসিসের চিকিৎসা এবং প্রতিরোধে প্রতিমাসে একটি **বনোভা®** ১৫০ মি.গ্রা. ট্যাবলেট সেব্য।

বিশেষক্ষেত্রে প্রয়োগমাত্রা ঃ

যকৃতের রোগীদের ক্ষেত্রে ঃ

প্রয়োগমাত্রায় কোন পরিবর্তন করার প্রয়োজন নেই।

সকালে ঘুম থেকে উঠে খাদ্য ও অন্য ওষুধ খাওয়ার কমপক্ষে ১ ঘন্টা আগে এক গ্লাস সাধারণ খাবার পানি দিয়ে খেতে হবে। **বনোভা®** খাওয়ার ১ ঘন্টার মধ্যে শোয়া যাবে না। এসময়টুকু বসে বা দাঁড়িয়ে বা স্বাভাবিক কাজ করে বা হেঁটে কাটানো যেতে পারে। কোন মাসের ডোজ বাদ পড়লে পরবর্তী ট্যাবলেট খাওয়ার দিনটি যদি অন্তত ৭ দিন পরে থাকে তবে মনে পড়ার পরের দিন সকালেই **বনোভা®** ১৫০ মি.গ্রা. ট্যাবলেট খেতে হবে এবং পরবর্তী ট্যাবলেট নির্ধারিত দিনেই খেতে হবে। কিন্তু পরবর্তী ট্যাবলেট খাওয়ার দিনটি ৭ দিনের মধ্যে হলে, ভুলে যাওয়া ডোজটি না খেয়ে পরবর্তী নির্ধারিত দিনেই ট্যাবলেটটি খেতে হবে। এক সপ্তাহে দুটি **বনোভা®** ১৫০ মি.গ্রা. ট্যাবলেট খাওয়া যাবে না।

সাবধানতা ঃ

হাইপোক্যালসেমিয়া এবং হাড় ও খনিজ পদার্থের বিপাকের সমস্যা চিকিৎসা করে **বনোভা®** থেরাপী শুরু করতে হবে। রোগীদের পর্যাপ্ত পরিমান ক্যালসিয়াম ও ভিটামিন ডি গ্রহণ গুরুত্বপূর্ণ এবং পরিপাকতন্ত্রের পার্শ্বপ্রতিক্রিয়ার ঝুঁকি কমাতে সেবনবিধি মেনে চলতে হবে।

সংরক্ষণ ঃ

ঠান্ডা এবং শুষ্ক স্থানে ৩০° সে. তাপমাত্রার নীচে সংরক্ষণ করুন।
সকল প্রকার ওষুধ শিশুদের নাগালের বাইরে রাখুন।

সরবরাহ ঃ

বনোভা® ১৫০ মি.গ্রাম. ট্যাবলেট: প্রতিটি বাক্সে রয়েছে ১টি ট্যাবলেটের ব্লিস্টার প্যাক।