Bonviva® 150 mg ATNAHS

film-coated tablet

1. NAME OF THE MEDICINAL PRODUCT

Bonviva 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg ibandronic acid (as ibandronic sodium monohydrate)

Excipients
Each film-coated tablet contains 162.75 mg lactose monohydrate. For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off white film-coated tablets, of oblong shape marked “BNVA” on one side, and “150” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see section 5.1). A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

The optimal duration of use of bisphosphates for the treatment of osteoporosis has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

4.2 Posology and method of administration

Posology
For oral use.
The recommended dose is one 150 mg film-coated tablet once a month.
The tablet should preferably be taken on the same date each month.
Bonviva should be taken after an overnight fast (at least 6 hours) and 1 hour before the first food or drink (other than water) of the day (see section 4.5) or any other oral medicinal products or supplementation (including calcium):

Method of administration
Tablets should be swallowed whole with a glass of plain water (180 to 240 ml) while the patients is sitting or standing in an upright position. Patients should not lie down for 1 hour after taking Bonviva.
- Plain water is the only drink that should be taken with Bonviva. 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.

In case a dose is missed, patients should be instructed to take one Bonviva 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 tablets within the same week.
Patients should receive supplemental calcium and / or vitamin D if dietary intake is inadequate (see section 4.4 and section 4.5).

Special populations
Patients with renal impairment
No dosage adjustment is necessary for patients with mild or moderate renal impairment where serum creatinine is equal or below 200 µmol/l (2.3 mg/dl) or where creatinine clearance is ≥ 30 ml/min. Bonviva is not recommended for use in patients who have a serum creatinine above 200 µmol/l (2.3 mg/dl) or who have a creatinine clearance (measured or estimated) below 30ml/min, because of limited clinical data available from studies including such patients. (see section 4.4 and section 5.2).

Patients with hepatic impairment
No dosage adjustment is required (see section 5.2).

Elderly population (≥ 65 years)
No dosage adjustment is required (see section 5.2).

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

4.3 Contraindications
- Patients with uncorrected hypocalcaemia (see section 4.4). As with all bisphosphonates indicated in the treatment of osteoporosis, pre-existing hypocalcaemia needs to be corrected before initiating therapy with Bonviva.
- Hypersensitivity to ibandronic acid or to any of the excipients listed in section 6.1.
- As with several bisphosphonates Bonviva is contraindicated in patients with abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia (see section 4.4).
- Bonviva is contraindicated in patients who are unable to stand or sit upright for at least 60 minutes (see sections 4.2 and 4.4).

4.4 Special warnings and special precautions for use

Hypocalcaemia
Hypocalcaemia must be corrected before starting Bonviva therapy.
Other disturbances of bone and mineral metabolism should also be effectively treated.
Adequate intake of calcium and vitamin D is important in all patients.

Gastrointestinal irritation
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 Bonviva 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, occasionally with bleeding and rarely 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 4.2).

Physicians should be alert to any signs or symptoms signalling a possible esophageal reaction and patients should be instructed to discontinue Bonviva 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 complication.

Since NSAIDS and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Renal impairment
Patients with concomitant diseases, or who use medicinal products which have potential for undesirable effects on the kidney, should be reviewed regularly in line with good medical practice during treatment.
Due to limited clinical experience, Bonviva is not recommended for patients with a serum creatinine above 200 µmol/l (2.3 mg/dl) or with a creatinine clearance below 30 ml/min. (see section 4.2 and section 5.2).

Osteonecrosis of the jaw
Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids.
Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.
A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy including angiogenesis inhibitors, radiotherapy, corticosteroids, poor oral hygiene).
While on treatment, these patients should avoid invasive dental procedures if possible. 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 osteonecrosis of the jaw.

Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Cases of osteonecrosis of other oro-facial sites including the external auditory canal have also been reported in patients treated with bisphosphonates including IBN. Risk factors are similar as for ONJ. Other risk factors may include repetitive minor trauma (e.g., habitual cotton bud use). The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Galactose intolerance
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures:
Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.
Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

4.5 Interaction with other medicinal products and other forms of interaction
Drug-Food Interactions
Oral bioavailability of ibandronic acid is generally reduced in the presence of food. In particular, products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk, are likely to interfere with absorption of Bonviva, which is consistent with findings in animal studies.
Therefore, patients should fast overnight (at least 6 hours) before taking Bonviva and continue fasting for 1 hour following intake of Bonviva (see section 4.2).

Drug-Drug Interactions
Calcium supplements, antacids and some oral medicinal products containing multivalent cations (such as aluminium, magnesium, iron) are likely to interfere with the absorption of Bonviva. Therefore, patients should not take other oral medicinal products for at least 6 hours before taking Bonviva and for 1 hour following intake of Bonviva.

Pharmacokinetic interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen). No interaction was observed when co-administered with melphalan/prednisolone in patients with multiple myeloma.

In healthy male volunteers and postmenopausal women, intravenous administration of 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 variability of the bioavailability of ibandronic acid, no dosage adjustment is considered necessary when Bonviva is administered with H2-antagonists or other active substances which increase gastric pH.

Metabolic interactions are not 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 (see section 5.2). Furthermore, plasma protein binding is approximately 85 % - 87 % (determined in vitro therapeutic drug concentrations), and thus there is a low potential for drug-drug interaction due to displacement. 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 active substances.

In a two-year study in postmenopausal women with osteoporosis (BM 16549), the incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking Bonviva 2.5 mg daily or 150 mg once monthly after one or two years.

Of over 1500 patients enrolled in study BM 16549 comparing monthly with daily dosing regimens of ibandronic acid, 14 % and 18 % of patients used histamine (H2) blockers or proton pump inhibitors after one and two years, respectively. Among these patients, the incidence of upper gastrointestinal events in the patients treated with Bonviva 150 mg once monthly was similar to that in patients treated with Bonviva 2.5 mg daily.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Bonviva should not be used during pregnancy.

Breast-feeding
It is not known whether ibandronic acid is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of ibandronic acid in the milk following intravenous administration. Bonviva should not be used during lactation.

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

4.8 Undesirable effects
Treatment of postmenopausal osteoporosis
Daily dosing
The safety of Bonviva 2.5 mg daily was evaluated in 1251 patients treated in 4 placebo-controlled clinical studies; 73 % of these patients came from the pivotal three-year treatment study (MF 4411). The overall safety profile of Bonviva 2.5 mg daily in all these studies was similar to that of placebo. The overall proportion of patients who experience an adverse drug reaction, i.e. adverse event with a possible or probable relationship to trial medication, in the pivotal treatment study (MF 4411) was 19.8 % for Bonviva and 17.9 % for placebo.

Once monthly dosing
In a two-year study in postmenopausal women with osteoporosis (BM 16549) the overall safety of Bonviva 150 mg once monthly and Bonviva 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 Bonviva 150 mg once monthly and 21.5 % and 22.5 % for Bonviva 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 1 % of patients treated with Bonviva 150 mg monthly or 2.5 mg daily in study BM 16549 and in patients treated with Bonviva 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.

MedDRA version 6.1
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	Bonviva 150mg once monthly (N=396) (%)	Bonviva 2.5 mg daily (N=395) (%)	Bonviva 2.5 mg daily (N=977) (%)	Placebo (N=975) (%)
Gastrointestinal system				
Dyspepsia	3.3	5.8	4.3	2.9
Nausea	3.3	3.5	1.8	2.3
Abdominal pain	3.5	2.8	2.1	2.9
Diarrhoea	2.5	1.8	1.4	1.0
Flatulence	0.5	1.0	0.4	0.7
Gastro-oesophageal reflux disease	0.5	1.0	0.4	0.1
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				
Myalgia	1.5	0.3	1.8	0.8
Arthralgia	1.0	0.3	0.4	0.4
Skin disorders				
Rash	0.8	1.0	1.2	0.7

*Transient, influenza-like symptoms have been reported with Bonviva 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	Bonviva 150mg once monthly (N=396) (%)	Bonviva 2.5 mg daily (N=395) (%)	Bonviva 2.5 mg daily (N=977) (%)	Placebo (N=975) (%)
Gastrointestinal system				
Dyspepsia	4.0	6.3	4.0	2.7
Nausea	3.0	3.5	1.8	2.3
Abdominal pain	4.0	3.0	2.1	2.9
Diarrhoea	2.5	2.0	1.4	1.0
Gastritis	1.0	0.3	0.7	0.5
Gastro-oesophageal reflux disease	0.8	1.0	0.5	0.1
Oesophagitis	0	1.0	0.5	0.4
Nervous system				
Headache	0.8	1.5	0.8	0.6
General disorders				
Influenza like illness*	3.3	0.3	0.3	0.2

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Bonviva® 150 mg ATNAHS
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	Two year cumulative data in study BM 16549		Three year data in study MF 4411	
System Organ Class/ Adverse drug reaction	Bonviva 150mg once monthly (N=396) (%)	Bonviva 2.5 mg daily (N=395) (%)	Bonviva 2.5 mg daily (N=977) (%)	Placebo (N=975) (%)
Musculoskeletal system				
Myalgia	1.5	0.3	1.8	0.8
Arthralgia	1.0	0.5	0.4	0.4
Muscle cramp	0.5	1.0	0.1	0.4
Musculoskeletal pain	1.0	0.5	0	0
Musculoskeletal stiffness	1.0	0	0	0
Skin disorders				
Rash	0.8	1.0	1.2	0.7

MedDRA version 7.1

*Transient, influenza-like symptoms have been reported with Bonviva 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.

Adverse drug reactions occurring at a frequency of less than or equal to 1%
The following list provides information on adverse drug reactions reported in study MF 4411 occurring more frequently with Bonviva 2.5 mg daily than with placebo and study BM 16549 occurring more frequently with Bonviva 150 mg once monthly than with Bonviva 2.5 mg daily. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Uncommon (1/100 – 1/1,000)
Gastro-intestinal Disorders: dysphagia, vomiting, gastritis, oesophagitis including oesophageal ulcerations or strictures.

Nervous System Disorders: dizziness
Musculoskeletal and Connective Tissue Disorders: back pain

Rare (1/1,000 – 1/10,000)
Gastro-intestinal Disorder: duodenitis
Immune System Disorders: hypersensitivity reactions
Skin and Subcutaneous Tissue Disorders: angioedema, face oedema, urticaria

Once monthly dosing
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.

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

Post-marketing Experience

Musculoskeletal and connective tissue disorders:
Osteonecrosis of the jaw and other oro-facial sites, including the external auditory canal, has been reported very rarely in patients treated with bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis.
Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4).

Injury, Poisoning and Procedural complications:
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, including ibandronic acid, however causality has not been established.

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

Immune system disorders:
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with ibandronic acid

Allergic reactions including asthma exacerbation have been reported.

Severe Cutaneous Adverse Reactions including Steven-Johnson Syndrome, Erythema Multiforme, and Bullous Dermatitis, have been reported.

4.9 Overdose
No specific information is available on the treatment of over dosage with Bonviva. However, based on a knowledge of this class of compounds, oral overdosage may result in upper gastrointestinal adverse reactions (such as upset stomach, dyspepsia, oesophagitis, gastritis, or ulcer) or hypocalcaemia. Milk or antacids should be given to bind Bonviva, and any adverse reactions treated symptomatically. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patients should remain fully upright.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Medicinal products for treatment of bone diseases, Bisphosphonates, ATC code: M05B A06

Mechanism of action
Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. 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 leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

Daily or intermittent administration of ibandronic acid results in reduced bone resorption as reflected in reduced levels of serum and urinary biochemical markers on bone turnover, increased BMD and a decreased incidence of fractures.

Pharmacodynamics effects
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, tumours or tumour extracts. In young (fast growing) rats, the endogenous bone resorption is also inhibited, leading to increased normal 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.

Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys was associated with formation of a new bone of normal quality and maintained or increased mechanical strength even at doses in the toxic range.

In human, 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 Bonviva demonstrated anti-fracture efficacy.

In animal models ibandronic acid 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 N-telopeptides of type I collagen (NTX)).

In a Phase 1 bioequivalence study conducted in 72 post-menopausal 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.

Clinical efficacy
Independent risk factors, for example, low BMD, age, the existence of previous fractures, a family history of fractures, high bone turnover and low body mass index should be considered in order to identify women at increased risk of osteoporotic fractures.

Bonviva 150 mg once monthly

Bone mineral density
Bonviva 150 mg once monthly was shown to be at least as effective as Bonviva 2.5 mg 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 (Pre-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 % [95% CI]	Bonviva 2.5 mg daily (N=318)	Bonviva 150 mg once monthly (N=320)	Bonviva 2.5 mg daily (N=294)	Bonviva 150 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, 7.1]
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, 4.5]	6.2 [5.7, 6.7]

Furthermore, Bonviva 150 mg once monthly was proven superior to Bonviva 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 Bonviva 150 mg once monthly had a lumbar spine BMD increase above or equal to baseline (BMD responders), compared with 84.0 % of patients receiving Bonviva 2.5 mg daily. At two years, 93.5 % (p=0.004) and 86.4 % of patients receiving Bonviva 150 mg once monthly or Bonviva 2.5 mg daily, respectively, were responders.

For total hip BMD, 90.0 % (p<0.001) of patients receiving Bonviva 150 mg once monthly and 76.7 % of patients receiving Bonviva 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 Bonviva 150 mg once monthly and 78.4 %, of patients receiving Bonviva 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 Bonviva 150 mg once monthly or Bonviva 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 Bonviva 150 mg once monthly and -67% for Bonviva 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 Bonviva 150 mg once monthly and 73.9% of patients receiving Bonviva 2.5 mg daily were identified as responders (defined as a decrease ≥50 % from baseline). At two years 78.7 % (p=0.002) 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, Bonviva 150 mg once monthly is expected to be at least as effective in preventing fractures as Bonviva 2.5 mg daily.

Bonviva 2.5 mg daily
In the initial three-year, randomised, 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 (table 4). In this study, Bonviva 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) as an exploratory regimen. Bonviva was taken 60 minutes before the first food or drink of the day (post-dose fasting period). The study enrolled women aged 55 to 80 years, who were at least 5 years postmenopausal, who had a BMD at lumbar spine of 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. Efficacy was evaluated in 2,928 patients.

Bonviva 2.5 mg administered daily, showed a statistically significant and medically relevant reduction in the incidence of new vertebral fractures. This regimen reduced the occurrence of new radiographic vertebral fractures by 62 % (p=0.0001) over the three year duration of the study. A relative risk reduction of 61 % was observed after 2 years (p=0.0006). No statistically significant difference was attained after 1 year of treatment (p=0.056). The anti-fracture effect was consistent over the duration of the study. There was no indication of a waning of the effect over time.

The incidence of clinical vertebral fractures was also significantly reduced by 49 % (p=0.011). The strong effect on vertebral fractures was furthermore reflected by a statistically significant reduction of height loss compared to placebo (p<0.0001).

Table 4: Results from 3 years fracture study MF 4411 (% 95 % CI)

	Placebo (N=974)	Bonviva 2.5 mg daily (N=977)
Relative Risk Reduction New morphometric vertebral fractures		62 % (40.9, 75.1)
Incidence of new morphometric vertebral fractures	9.56 % (7.5, 11.7)	4.68 % (3.2, 6.2)
Relative risk reduction of clinical vertebral fracture		49 % (14.03, 69.49)
Incidence of clinical vertebral fracture	5.33 % (3.73, 6.92)	2.75 % (1.61, 3.89)
BMD – mean change relative to baseline lumbar spine at year 3	1.26 % (0.8, 1.7)	6.54 % (6.1, 7.0)
BMD – mean change relative to baseline total hip at year 3	-0.69 % (-1.0, -0.4)	3.36 % (3.0, 3.7)

The treatment effect of Bonviva was further assessed in an analysis of the subpopulation of patients who at baseline had a lumbar spine BMD T-score below -2.5. The vertebral fracture risk reduction was very consistent with that seen in the overall population.

Table 5: Results from 3 years fracture study MF 4411 (% 95 % CI) for patients with lumbar spine BMD T-score below -2.5 at baseline

	Placebo (N=587)	Bonviva 2.5 mg daily (N=575)
Relative Risk Reduction New morphometric vertebral fractures		59 % (34.5, 74.3)
Incidence of new morphometric vertebral fractures	12.54 % (9.53, 15.55)	5.36 % (3.31, 7.41)
Relative risk reduction of clinical vertebral fracture		50 % (9.49, 71.91)
Incidence of clinical vertebral fracture	6.97 % (4.67, 9.27)	3.57 % (1.89, 5.24)
BMD – mean change relative to baseline lumbar spine at year 3	1.13 % (0.6, 1.7)	7.01 % (6.5, 7.6)
BMD – mean change relative to baseline total hip at year 3	-0.70 % (-1.1, -0.2)	3.59 % (3.1, 4.1)

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 nonvertebral fractures in a subgroup of patients being at higher fracture risk (femoral neck BMD T–score <–3.0 SD). However, a risk reduction in non-vertebral fractures was not observed in other subgroups. The observation of non-vertebral fracture efficacy in high-risk subgroups is consistent with clinical trial findings for other bisphosphonates.

Daily treatment with 2.5 mg resulted in progressive increases in BMD at vertebral and nonvertebral sites of the skeleton. Three-year lumbar spine BMD increase compared to placebo was 5.3 % and 6.5 % compared to baseline.

Increases at the hip compared to baseline were 2.8 % at the femoral neck, 3.4 % at the total hip, and 5.5 % at the trochanter. 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 Bonviva 2.5 mg daily and 20 mg intermittently, respectively. Decreases in biochemical markers of bone resorption were evident within 7 days of starting treatment.

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.

5.2 Pharmacokinetic properties
The primary pharmacological effects of ibandronic acid on bone are not directly related to actual plasma concentrations, as demonstrated by various studies in animals and 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.

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

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 % - 87 % (determined in vitro at therapeutic drug concentration, and thus there is a low potential for drug-drug interaction due to displacement.

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

Elimination
The absorbed fraction of ibandronic acid is removed from the circulation via bone absorption (estimated to be 40 – 50 % in postmenopausal women) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid is eliminated unchanged in the faeces.

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. As the values calculated are largely a function of the duration of study, the dose used, and assay sensitivity, the true terminal half-life is likely to be substantially longer, in common with other bisphosphonates. 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/min.

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 clearance is considered to reflect the uptake by bone.

Pharmacokinetics in special clinical situations

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

Race
There is no evidence for any clinically relevant inter-ethnic differences between Asians and Caucasians in ibandronic acid disposition. There is limited data available on patients of African origin.

Patients with renal impairment
Renal clearance of ibandronic acid in patients with various degree of renal impairment is linearly related to creatinine clearance. No dose adjustment is necessary for patients with mild or moderate renal impairment (CLcr equal or greater than 30 ml/min), as show in study BM16549 where the majority of patients had mild to moderate renal impairment.

Subjects with severe renal failure (CLcr < 30 ml/min) receiving daily oral administration of 10 mg ibandronic acid for 21 days, had 2-3 fold higher plasma concentrations than subjects with normal renal function and total clearance of ibandronic acid was 44 ml/min. After intravenous administration of 0.5 mg, total, renal, and non-renal clearances decreased by 67 %, 77 % and 50 %, respectively, in subjects with severe renal failure but there was no reduction in tolerability associated with the increase in exposure.
Due to the limited clinical experience, Bonviva is not recommended in patients with severe renal impairment (see section 4.2 and section 4.4). The pharmacokinetics of ibandronic acid was not assessed in patients with end-stage renal disease managed by other than hemodialysis. The pharmacokinetics of ibandronic acid in these patients is unknown, and ibandronic acid should not be used under these circumstances.

Patients with hepatic impairment (see section 4.2)
There is no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid which is not metabolised but is cleared by renal excretion and by uptake into bone. Therefore dosage adjustment is not necessary in patients with hepatic impairment. Further, as protein binding of ibandronic acid is low (85%) at therapeutic concentrations, hypoproteinemia in severe liver disease is unlikely to lead to clinically significant increases in free plasma concentration.

Elderly (see section 4.2)
In a multivariate analysis, age was not found to be an independent factor of any of the pharmacokinetic parameters studied. As renal function decreases with age this is the only factor to take into consideration (see renal impairment section).

Children and adolescents (see section 4.2 and section 5.1)
There is no data on the use of Bonviva in patients less than 18 years old.

5.3 Preclinical safety data
Toxic effects, e.g signs of renal damage, were observed in dogs only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Mutagenicity/Carcinogenicity:
No indication of carcinogenic potential was observed. Test for genotoxicity revealed no evidence of genetic activity for ibandronic acid.

Reproductive toxicity:
There was no evidence for a direct foetal toxic or teratogenic effect of ibandronic acid in orally treated rats and rabbits and there were no adverse effects on the development in F1 offspring in rats at an extrapolated exposure of at least 35 times above human exposure.

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 Bonviva in pregnant women.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate, Povidone, Microcrystalline Cellulose, Crospovidone, Stearic acid, Colloidal anhydrous Silica

Tablet coat
Hypromellose, Titanium dioxide E171, Talc, Macrogol 6,000

6.2 Incompatibilities
Not applicable.

6.3 nature and contents of container
Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC) containing 1 or 3 tablets. Not all pack sizes may be marketed.

6.4 Instructions for use and handling
No special requirements.

Product Owner
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