Bonviva®
Ibandronic acid
Pre-filled Syringe 3 mg/3ml

1. NAME OF THE MEDICINAL PRODUCT
Bonviva 3 mg/3ml solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One pre-filled syringe of 3 ml solution contains 3 mg ibandronic acid (as 3.375 mg ibandronic acid, monosodium salt, monohydrate).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection, pre-filled syringe.
Clear, colourless solution.

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 bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefit and potential risks of Bonviva on an individual patient basis, particularly after 5 or more years of use.

4.2 Posology and method of administration
For intravenous use.

Posology
The recommended dose of ibandronic acid is 3 mg, administered as an intravenous injection over 15 - 30 seconds, every three months.

Strict adherence to the intravenous administration route is required (see section 4.4).
Patients must receive supplemental calcium and vitamin D (see section 4.4 and section 4.5)
If a dose is missed, the injection should be administered as soon as convenient. Thereafter, injections should be scheduled every 3 months from the date of the last injection.

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 (measured or estimated) is equal or greater than 30 ml/min.

Bonviva injection 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 30 ml/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)
- Hypersensitivity to ibandronic acid or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypocalcaemia
Bonviva, like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values.

Existing hypocalcaemia must be corrected before starting Bonviva injection therapy. Other disturbances of bone and mineral metabolism should also be effectively treated before starting Bonviva injection therapy.

All patients must receive adequate supplemental calcium and vitamin D.

Administration failures
Strict adherence to the intravenous route of administration is required. Care must be taken not to administer Bonviva injection via intra-arterial or paravenous administration as this could lead to tissue damage.

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 injection 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.

Anaphylactic reaction/shock
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with intravenous ibandronic acid.

Appropriate medical support and monitoring measures should be readily available when Bonviva intravenous injection is administered.

If anaphylactic or other severe hypersensitivity/allergic reaction occur, immediately discontinue the injection and initiate appropriate treatment.

Patients with cardiac impairment
Overhydration should be avoided in patients at risk of cardiac failure.

Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Bonviva is essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction
Drug-Drug Interactions
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 at therapeutic ibandronic acid 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.

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.

4.6 Fertility, pregnancy and lactation

Bonviva should not be used during pregnancy and lactation.

Pregnancy
Bonviva is only for use in postmenopausal women and must not be taken by women of child bearing potential.

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.

There is no clinical experience with Bonviva in pregnant women.

Breast-feeding
It is not known whether Bonviva 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.

Fertility
There are no data on the effects of ibandronic acid from humans. In reproductive studies in rats by the oral route, ibandronic acid decreased fertility. In studies in rats using the intravenous route, ibandronic acid decreased fertility at high daily doses (see section 5.3).

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
2.5 mg daily oral dosing
The safety of oral treatment with Bonviva 2.5 mg once 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 experienced an adverse reaction, i.e. adverse event with a possible or probable relationship to trial medicinal product, in the pivotal treatment study (MF 4411) was 19.8 % for Bonviva and 17.9 % for placebo.

3 mg every 3 months i.v. dosing
In the pivotal two-year study in postmenopausal women with osteoporosis (BM16550), the overall safety of intravenous injection of Bonviva 3 mg every 3 months and oral Bonviva 2.5 mg daily were shown to be similar. The overall proportion of patients who experienced an adverse reaction was 26.0 % and 28.6 % for Bonviva 3 mg injection every 3 months and 20.4 % and 22.6 % for oral Bonviva

2.5 mg daily after one year and two years, respectively. The majority of adverse reactions were mild to moderate in intensity. Most cases of adverse reactions did not lead to cessation of therapy.

Table 1 and table 2 list adverse events after one year and two years of treatment, respectively, from the pivotal phase III trial BM16550, reported as possibly or probably related to trial medicinal product, in more than 1 % of the patients treated with either intravenous injection of Bonviva 3 mg every 3 months or intravenous injection of placebo plus oral Bonviva 2.5 mg daily. Adverse drug reactions reported in patients treated with Bonviva 3 mg injection at a frequency equal to or less than that in orally treated patients, are not included. Tables 1 and 2 also show adverse reactions in patients treated for 3 years with oral Bonviva 2.5 mg daily in the anti-fracture study (MF4411). For both studies, adverse reactions are listed which occurred with a higher incidence in Bonviva-treated patients compared with the placebo-treated patients of study MF4411. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Common adverse reactions (>1/100, ≤ 1/10) in the phase III osteoporosis study BM16550 after one year of treatment and in the phase III anti-fracture study MF 4411 (three-year study), that were considered by the investigator to be possibly or probably related to study medicinal product.

	One year data in study BM 16550		**Three year data in study MF 4411**	
System Organ Class/Adverse reaction	Bonviva injection 3 mg every 3 months (N=469) ADR No. (%)	Placebo injection + oral Bonviva 2.5 mg daily (N=465) ADR No. (%)	Oral Bonviva 2.5 mg daily (N=977) ADR No. (%)	Placebo (N=975) ADR No. (%)
Gastrointestinal disorders				
Gastritis	5 (1.1)	4 (0.9)	7 (0.7)	5 (0.5)
Diarrhoea	5 (1.1)	2 (0.4)	14 (1.4)	10 (1.0)
Abdominal pain	13 (2.8)	15 (3.2)	21 (2.1)	28 (2.9)
Dyspepsia	12 (2.6)	18 (3.9)	40 (4.1)	26 (2.7)
Nausea	8 (1.7)	12 (2.6)	18 (1.8)	22 (2.3)
Constipation	5 (1.1)	7 (1.5)	3 (0.3)	9 (0.9)
Musculoskeletal disorders				
Musculoskeletal pain	5 (1.1)	2 (0.4)	-	-
Arthralgia	11 (2.3)	4 (0.9)	4 (0.4)	4 (0.4)
Myalgia	8 (1.7)	4 (0.9)	18 (1.8)	8 (0.8)
General System Disorders				
Influenza-like illness*	22 (4.7)	4 (0.9)	3 (0.3)	2 (0.2)
Fatigue	5 (1.1)	2 (0.4)	3 (0.3)	4 (0.4)
Nervous System Disorders				
Headache	5 (1.1)	3 (0.6)	8 (0.8)	6 (0.6)
Skin disorders				
Rash	4 (0.9)	3 (0.6)	12 (1.2)	7 (0.7)

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* Transient, influenza-like symptoms have been reported in patients receiving intravenous injection of Bonviva 3 mg every 3 months, typically in association with the first dose.
Influenza-like illness includes events reported as acute phase reaction or symptoms, including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, and bone pain. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures.

Table 2: Common adverse reactions (>1/100, ≤ 1/10) in the phase III osteoporosis study BM16550 after two years of treatment (cumulative data) and in the phase III anti-fracture study MF 4411 (three-year study), that were considered by the investigator to be possibly or probably related to study medicinal product.

	Two year data in study BM 16550		**Three year data in study MF 4411**	
System Organ Class/Adverse reaction	Bonviva injection 3 mg every 3 months (N=469) ADR No. (%)	Placebo injection + oral Bonviva 2.5 mg daily (N=465) ADR No. (%)	Oral Bonviva 2.5 mg daily (N=977) ADR No. (%)	Placebo (N=975) ADR No. (%)
Gastrointestinal disorders				
Gastritis	6 (1.3)	4 (0.9)	7 (0.7)	5 (0.5)
Diarrhoea	5 (1.1)	3 (0.6)	14 (1.4)	10 (1.0)
Abdominal pain	17 (3.6)	21 (4.5)	21 (2.1)	28 (2.9)
Dyspepsia	14 (3.0)	19 (4.1)	40 (4.1)	26 (2.7)
Nausea	8 (1.7)	13 (2.8)	18 (1.8)	22 (2.3)
Constipation	5 (1.1)	7 (1.5)	3 (0.3)	9 (0.9)
Musculoskeletal disorders				
Musculoskeletal pain	5 (1.1)	2 (0.4)	-	-
Arthralgia	13 (2.8)	4 (0.9)	4 (0.4)	4 (0.4)
Myalgia	8 (1.7)	4 (0.9)	18 (1.8)	8 (0.8)
Back pain	5 (1.1)	1 (0.2)	3 (0.3)	2 (0.2)
General System Disorders				
Influenza-like illness*	21 (4.5)	4 (0.9)	3 (0.3)	2 (0.2)
Fatigue	5 (1.1)	2 (0.4)	3 (0.3)	4 (0.4)
Nervous System Disorders				
Headache	6 (1.3)	3 (0.6)	8 (0.8)	6 (0.6)
Skin disorders				
Rash	4 (0.9)	4 (0.9)	12 (1.2)	7 (0.7)

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* Transient, influenza-like symptoms have been reported in patients receiving intravenous injection of Bonviva 3 mg every 3 months, typically in association with the first dose.

Influenza-like illness includes events reported as acute phase reaction or symptoms, including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, and bone pain. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures.

Adverse reactions occurring at a frequency of ≤ 1 % in study BM16650 that were considered by the investigator to be possibly or probably related to study medicinal product:

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Uncommon (> 1/1,000 and < 1/100)	
Musculoskeletal disorders	Bone pain
General disorders and administration site conditions	Asthenia Injection site reactions
Vascular disorders	Phlebitis/thrombophlebitis
Rare (> 1/10,000 and < 1/1,000)	
Immune system disorders	Hypersensitivity reactions
Skin and subcutaneous tissue disorders	Angioedema Facial swelling/oedema Urticarial

Laboratory test findings

In the pivotal three-year study with oral Bonviva 2.5 mg daily (MF 4411) there was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, impaired haematologic system, hypocalcaemia or hypophosphataemia. Similarly, no differences were noted between the groups in the pivotal study with Bonviva 3 mg injection every 3 months (BM 16550).

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 in patients treated by 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 fracture 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 bisphosphonates, including ibandronic acid. In some cases, these events did not resolve until the bisphosphonate was discontinued.

Immune system disorders:
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with ibandronic acid (see section 4.4).

Allergic reactions including asthma exacerbation have been reported.

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

4.9 Overdose
No specific information is available on the treatment of overdosage with Bonviva.
Based on knowledge of this class of compounds, intravenous overdosage may result in hypocalcaemia, hypophosphataemia, and hypomagnesaemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

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 oral ibandronic acid results in reduced bone resorption as reflected in reduced levels of serum and urinary biochemical markers of bone turnover, increased bone mineral density BMD and a decreased incidence of fractures.

Pharmacodynamic effects
The pharmacodynamic action of ibandronic acid is inhibition of bone resorption. In vivo, ibandronic acid prevents bone destruction experimentally induced 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 mineralisation 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 new bone of normal quality and maintained or

increased mechanical strength even at doses in 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 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)). Both daily, intermittent (with a dose-free interval of 9 - 10 weeks per quarter) oral doses as well as intravenous doses of Bonviva in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption.

Bonviva intravenous injection decreased levels of serum C-telopeptide of the alpha chain of Type I collagen (CTX) within 3 - 7 days of starting treatment and decreased levels of osteocalcin within 3 months.

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 with doses of oral Bonviva 2.5 mg daily and intermittent intravenous doses of up to 1 mg every 3 months showed bone of normal quality and no indication of a mineralisation defect. An expected decrease in bone turnover, normal quality of bone and absence of defects in mineralization were also seen after two years of treatment with Bonviva 3 mg injection.

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 3 mg injection every 3 months
Bone mineral density (BMD)
Bonviva 3 mg intravenous injection, administered every 3 months, was shown to be at least as effective as oral Bonviva 2.5 mg daily in a 2-year, randomised, double-blind, multicentre, non-inferiority study (BM16550) of postmenopausal women (1386 women aged 55 - 80) with osteoporosis (lumbar spine BMD T-score below -2.5 SD at baseline). All patients received 400 IU vitamin D and 500 mg calcium supplementation per day. This was demonstrated in both the primary analysis at one year and in the confirmatory analysis at two years endpoint (Table 3).
The primary analysis of data from study BM16550 at one year and the confirmatory analysis at 2 years demonstrated the non-inferiority of 3 mg every 3 months injection dosing regimen compared to 2.5 mg oral daily dosing regimen, in terms of mean increases in BMD at lumbar spine, total hip, femoral neck and trochanter (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 16550.

	One year data in study BM 16550		**Two year data in study BM 16550**	
Mean relative changes from [baseline % 95% CI]	Bonviva 2.5 mg daily (N=377)	Bonviva 3 mg injection every 3 months (N=365)	Bonviva 2.5 mg daily (N=334)	Bonviva 3 mg injection every 3 months (N=334)
Lumbar spine L2-L4	3.8 [3.4, 4.2]	4.8 [4.5, 5.2]	4.8 [4.3, 5.4]	6.3 [5.7, 6.8]

BMD				
Total hip BMD	1.8 [1.5, 2.1]	2.4 [2.0, 2.7]	2.2 [1.8, 2.6]	3.1 [2.6, 3.6]
Femoral neck BMD	1.6 [1.2, 2.0]	2.3 [1.9, 2.7]	2.2 [1.8, 2.7]	2.8 [2.3, 3.3]
Trochanter BMD	3.0 [2.6, 3.4]	3.8 [3.2, 4.4]	3.5 [3.0, 4.0]	4.9 [4.1, 5.7]

Furthermore, Bonviva 3 mg injection every 3 months was proven superior to oral Bonviva 2.5 mg daily for increases in lumbar spine BMD in a prospectively planned analysis at one year, p<0.001, and at two years, p<0.001.

For lumbar spine BMD, 92.1 % of patients receiving 3 mg injection every 3 months increased or maintained their BMD after 1 year of treatment (i.e. were responders) compared with 84.9 % of patients receiving oral 2.5 mg daily (p=0.002). After 2 years of treatment, 92.8 % of patients receiving 3 mg injections and 84.7 % of patient receiving 2.5 mg oral therapy had increased or maintained lumbar spine BMD (p=0.001).

For total hip BMD, 82.3 % of patients receiving 3 mg injection every 3 months were responders at one year, compared with 75.1 % of patients receiving 2.5 mg daily orally (p=0.02). After 2 years of treatment, 85.6 % of patients receiving 3 mg injections and 77.0 % of patient receiving 2.5 mg oral therapy had increased or maintained total hip BMD (p=0.004).
The proportion of patients who increased or maintained their BMD at one year at both lumbar spine and total hip was 76.2 % in the 3 mg injection every 3 months arm and 67.2 % in the 2.5 mg daily orally arm (p=0.007). At two years, 80.1% and 68.8 % of patients met this criterion in the 3 mg every 3 months injection arm and the 2.5 mg daily arm (p=0.001).

Biochemical markers of bone turn-over
Clinically meaningful reductions in serum CTX levels were observed at all time points measured. At 12 months median relative changes from baseline were –58.6 % for the intravenous injection of 3 mg every 3 months regimen and –62.6 % for oral 2.5 mg daily regimen. In addition, 64.8 % of patients receiving 3 mg every 3 months injection were identified as responders (defined as a decrease ≥ 50 % from baseline), compared with 64.9 % of patients receiving 2.5 mg daily orally. Serum CTX reduction was maintained over the 2 years, with more than half of the patients identified as responders in both treatment groups.

Based on the results of study BM 16550, Bonviva 3 mg intravenous injection, administered every 3 months is expected to be at least as effective in preventing fractures as the oral regimen of Bonviva 2.5 mg daily.

Bonviva 2.5 mg daily tablets
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 the 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 % after 3 years (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 fracture	9.56% (7.5, 11.7)	4.68% (3.2, 6.2)
Relative risk reduction of clinical vertebral fracture		49% (14.03, 69.43)
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 (table 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 fracture	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 fracture was observed for non-vertebral 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 oral treatment with Bonviva 2.5 mg tablets 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 of using 2.5 mg Bonviva daily.

A clinically meaningful reduction of 50 % of biochemical markers of bone resorption was observed as early as one month after starting treatment with Bonviva 2.5 mg. Decreases in biochemical markers of bone resorption were evident within 7 days of starting treatment.

Paediatric population (see section 4.2 and section 5.2)

Bonviva was not studied in the paediatric population, therefore no efficacy or safety data are available for this patient population.

5.2 Pharmacokinetic properties
The primary pharmacological effects of ibandronic acid are not directly related to actual plasma concentrations as the site of action is in bone. This was 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.

Plasma concentrations of ibandronic acid increase in a dose-proportional manner after intravenous administration of 0.5 mg to 6 mg.

Absorption
Not applicable

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 approximately 85 % - 87 % (determined in vitro at therapeutic ibandronic acid concentrations), 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
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 range of observed apparent half-lives is broad, 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 the 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 clearances is considered to reflect the uptake by bone.

The secretory pathway appears not to include known acidic or basic transport systems involved in the excretion of other active substances (see section 4.5). In addition, ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and does not induce the hepatic cytochrome P450 system in rats.

Pharmacokinetics in special clinical situations
Gender
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 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 equal or above 30 ml/min).

Subjects with severe renal impairment (CLcr less than 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 of ibandronic acid, 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 in patients with end-stage renal disease was only assessed in a small number of patients managed by haemodialysis, therefore, the pharmacokinetics of ibandronic acid in the patients not undergoing haemodialysis is unknown. Due to the limited data available, ibandronic acid should not be used in all patients with end-stage renal disease.

Patients with hepatic impairment (see section 4.2)
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, 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 ibandronate 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. Since ibandronic acid is known not to be metabolised the only difference in ibandronic acid elimination for geriatric patients versus younger patients is expected to relate to age-related changes in renal function. As renal function decreases with age, renal function is the only factor to take into consideration (see renal impairment section). No dose adjustment is necessary based on age.

Children and adolescents (see section 4.2 and section 5.1)
There are 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 and genotoxic potential has been observed.

Reproductive toxicity:

Specific studies for the 3-monthly dosing regimen have not been performed. In studies with daily i.v. dosing regimen, there was no evidence for a direct foetal toxic or teratogenic effect of ibandronic acid in rats and rabbits. Body weight gain was decreased in F1 offspring in rats. In reproductive studies in rats by the oral route effects on fertility consisted of increased preimplantation losses at dose levels of 1 mg/kg/day and higher. In reproductive studies in rats by the intravenous route, ibandronic acid decreased sperm counts at doses of 0.3 and 1 mg/kg/day and decreased fertility in males at 1 mg/kg/day and in females 1.2 mg/kg/day. Other adverse reactions to 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Glacial acetic acid
Sodium acetate trihydrate
Water for injections

6.2 Incompatibilities

Bonviva solution for injection must not be mixed with calcium-containing solutions or other intravenously administered medicinal products.

6.3 Nature and contents of container

Pre-filled syringes (5 ml) made of colourless type I glass, the grey rubber plunger stopper and tip cap are made of fluororesin-laminated butyl rubber, containing 3 ml of solution for injection.
Packs of 1 pre-filled syringe and 1 injection needle or 4 pre-filled syringes and 4 injection needles.
Not all pack sizes may be marketed.

6.4 Special instructions for use, handling and disposal

The injection is for single use only. Only syringes containing a clear solution without particles should be used.

Strict adherence to the intravenous route of administration is recommended.

Where the product is administered into an existing intravenous infusion line, the infusate should be restricted to either isotonic saline or 50 mg/ml (5 %) glucose solution. This also applies to solutions used to flush butterfly and other devices.

Any unused solution for injection, syringe and injection needle should be disposed of in accordance with local requirements. The release of pharmaceuticals in the environment should be minimized.

Disposal of syringes/sharps:

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare professional.

For home use, a puncture resistant container for the disposal of used syringes and needles should be supplied to the patients.

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.

Storage condition: Store below 30 °C

Shelf life: 24 months

Marketing Authorization Holder:
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