PK.735-6546 APRIL WM

Bonviva® 3mg/3ml (Ibandronic acid) Solution for I.V. injection

بون ویوا® 3 ملی گرام/3 ملی لیٹر سوئٹزرلینڈ سے آئی۔ وی انجکشن

ATNAHS

Bisphosphonate – Drugs for treatment of bone diseases (M05)

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug
Bonviva is a nitrogen-containing bisphosphonate.

1.2 Type of Dosage Form
Pre-filled syringe.

1.3 Route of Administration
Intravenous.

1.4 Sterile / Radioactive Statement
Sterile product.

1.5 Qualitative and Quantitative Composition
Active ingredient:
Ibandronic acid, mono-sodium salt, monohydrate (Roche) eq. to Ibandronic acid.

Solution for injection:
Each pre-filled syringe contains:
Ibandronic acid, mono-sodium salt, monohydrate (Roche) eq. to Ibandronic acid....3mg/3ml

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)
Bonviva 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 Bonviva for treatment is 3 mg intravenous injection (administered as an intravenous injection over 15-30 seconds) every three months.

Patients must receive supplemental calcium and vitamin D.

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.

2.2.1 Special Dosage Instructions
Patients with hepatic impairment
No dosage adjustment is necessary (see section 3.2.4 Pharmacokinetics in Special Populations).

Patients with renal impairment
No dosage adjustment is necessary for patients with serum creatinine ≤ 200 µmol/l (2.3 mg/dl) or where creatinine clearance (measured or estimated) ≥ 30 ml/min.

Bonviva 3 mg every 3 months i.v. is not recommended for use in patients who have a serum creatinine >200 µmol/l (2.3 mg/dl) or who have a creatinine clearance (measured or estimated) < 30 ml/min because no clinical data are available from studies including such patients (see section 3.2.4 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
Bonviva is contraindicated in patients with known hypersensitivity to ibandronic acid or to any of the excipients.

Bonviva 3 mg every 3 months i.v. is contraindicated in patients with uncorrected hypocalcemia.

2.4 Warnings and Precautions

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

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Bonviva injection therapy. Adequate intake of calcium and vitamin D is important in all patients. Patients must receive supplemental calcium and vitamin D.

Bonviva 3 mg every 3 months i.v. is not recommended for use in patients who have a serum creatinine >200 µmol/l (2.3 mg/dl) or who have a creatinine clearance (measured or estimated) < 30 ml/min because no clinical data are available from studies including such patients (see section 3.2.4 Pharmacokinetics in Special Populations). Patients with concomitant diseases or medications which have potential for adverse effects on the kidney should be reviewed regularly in line with good medical practice during treatment.

	One-year study (BM 16550)		Three-year study (MF 4411)	
System Organ Class/Adverse drug reaction	**Bonviva 3 mg every 3 months i.v. (N=469) ADR No. (%)**	**Placebo i.v. injection + Bonviva 2.5 mg daily (N=465) ADR No. (%)**	**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)
Abdominal pain	13 (2.8)	15 (3.2)	21 (2.1)	28 (2.9)

Care must be taken not to administer Bonviva via intra-arterial administration or paravenous administration as this could lead to tissue damage.

Osteonecrosis of the jaw has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with post-menopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis of the jaw include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, 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 (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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.

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-Drug Interactions
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.

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 intravenous ibandronic acid was co-administered with melphalan/prednisolone in patients with multiple myeloma.

2.5 Use in Special Populations

2.5.1 Pregnancy
Bonviva should not be used during pregnancy and lactation.

Pregnancy
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 fetal toxic or teratogenic effect of ibandronic acid in rats and rabbits. Body weight gain was decreased in F1 offspring in rats. Other 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).

There is no clinical experience with Bonviva in pregnant women.

2.5.2 Nursing Mothers
Lactation
In lactating rats treated with 0.08 mg/kg/day i.v. 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 Bonviva is excreted in human milk.

2.5.3 Paediatric 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

2.5mg daily oral 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 experienced 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.

3mg 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 drug 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 drug reactions were mild to moderate in intensity. Most cases of adverse drug 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 drug reactions in patients treated for 3 years with oral Bonviva 2.5 mg daily in the anti-fracture study (MF4411). For both studies, adverse drug 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 drug 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 study (BM 16550)		Three-year study (MF 4411)	
System Organ Class/ Adverse drug reaction	**Bonviva 3 mg every 3 months i.v. (N=469) ADR No. (%)**	**Placebo i.v. injection + Bonviva 2.5 mg daily (N=465) ADR No. (%)**	**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)
Dyspepsia Nausea	12 (2.6)	18 (3.9)	40 (4.1)	26 (2.7)
Constipation Diarrhea	8 (1.7)	12 (2.6)	18 (1.8)	22 (2.3)
Musculoskeletal disorders				
Arthralgia	5 (1.1)	7 (1.5)	3 (0.3)	9 (0.9)
Myalgia	5 (1.1)	2 (0.4)	14 (1.4)	10 (1.0)
Musculo-skeletal pain	11 (2.3)	4 (0.9)	4 (0.4)	4 (0.4)
General system disorders				
Influenza-like illness*	8 (1.7)	4 (0.9)	18 (1.8)	8 (0.8)
Fatigue	5 (1.1)	2 (0.4)	-	-
Nervous system disorders				
Headache	22 (4.7)	4 (0.9)	3 (0.3)	2 (0.2)
Skin disorders				
Rash	5 (1.1)	2 (0.4)	3 (0.3)	4 (0.4)

MedDRA version 7.0
* 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 drug 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 drug 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				
Musculo-skeletal 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)

MedDRA version 8.0

* 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 drug 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
Vascular Disorders: Injection site reactions
Phlebitis/thrombophlebitis

Rare (>1/10,000 and <1/1,000)
Immune system disorders: Hypersensitivity reactions
Skin and subcutaneous tissue disorders: Angioedema
Facial swelling/ oedema
Urticaria

2.6.1.1 Laboratory Abnormalities

There was no evidence that Bonviva 3 mg every 3 months i.v. induced laboratory abnormalities indicative of hepatic or renal dysfunction, impaired hematologic system, hypocalcemia or hypophosphatemia.

2.6.2 Post Marketing
Musculoskeletal and connective tissue disorders:
Osteonecrosis of the jaw and of other oro-facial sites, including the external auditory canal, has been reported very rarely in patients treated with ibandronic acid (see section 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.

Immune system disorders:
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with ibandronic acid (see section 2.4 Warnings and Precautions). Allergic reactions including asthma exacerbation have been reported.

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

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

2.7 Overdose
No specific information is available on the treatment of over dosage with Bonviva.

Based on knowledge of this class of compounds, intravenous over dosage may result in hypocalcemia, hypophosphatemia, and hypomagnesemia. 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.

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 oral 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.

Both daily, intermittent (with a drug-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 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 Bonviva 2.5 mg daily and intermittent i.v. doses of up to 1 mg every 3 months showed bone of normal quality and no indication of a mineralization defect.

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. Ibandronate 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 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.

3.1.2 Clinical / Efficacy Studies
Treatment of postmenopausal osteoporosis

Bonviva 2.5mg daily
A statistically significant and medically relevant decrease in the incidence of new radiographic morphometric and clinical vertebral fractures was demonstrated in a 3-year, randomized, double-blind, placebo-controlled, fracture study (MF 4411). 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). Bonviva 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.

Bonviva 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 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.

Bonviva3mg every3months
The efficacy of Bonviva 3 mg every 3 months i.v. was demonstrated in a randomized, double-blind, multinational, non-inferiority trial (BM16550) in 1386 women aged 55-80 with postmenopausal osteoporosis (lumbar spine BMD, T score below -2.5 SD). All patients received 400 IU vitamin D and 500 mg calcium supplementation per day.

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 BMD	**3.8 [3.4, 4.2]**	**4.8 [4.5, 5.2]**	**4.8 [4.3, 5.4]**	**6.3 [5.7, 6.8]**
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

3.2 Pharmacokinetic Properties
The 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 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.

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

3.2.1 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.

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

3.2.3 Elimination
Following intravenous administration, ibandronic acid is removed from the circulation via bone absorption (40-50%) and the remainder is eliminated unchanged by the kidney.

The range of observed apparent half-lives is 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 an 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.

3.2.4 Pharmacokinetics in Special Populations
Gender
The 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 ml/min).

In subjects with severe renal impairment (CLcr ≤ 30 ml/min) receiving i.v. administration of 0.5 mg, total, renal, and non-renal clearances decreased by 67%, 77% and 50%, respectively. 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 which is not metabolized 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
Since ibandronic acid is known not to be metabolized the only difference in ibandronic acid elimination for geriatric patients versus younger patients is expected to relate to age-related changes in renal function (see chapter "Patients with renal impairment").
No dose adjustment is necessary based on age.

Children
There are no data on the use of Bonviva in patients less than 18 years old.

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 and genotoxic potential has been observed.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage
The product must be stored according to local climatic zone requirements

4.2 Incompatibilities
Bonviva should not be mixed with calcium-containing solutions or other intravenously administered drugs.

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

4.4 INSTRUCTIONS
Keep all medicines out of the reach of children. Protect from light, heat and moisture. Store below 30°C.

To be sold on prescription of a registered medical practitioner only.

4.5 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 via "piggyback" into an i.v. infusion line, the i.v. infusate should be restricted to either isotonic saline or 5% dextrose solution.

Unused solution for injection, syringe and needle should be discarded in accordance with local requirements.

4.6 Packs
3mg/3ml pre-filled syringe
Bonviva is supplied in the following dosage form , strength and pack size.
Solution for I.V. injection 3mg/3ml 1's

Manufactured by: Vetter Pharma- Fertigung GmbH & Co KG, Langenargen, Germany
Under licence from: Atnahs Pharma UK Ltd, Basildon United Kingdom
Imported and Marketed by:
Martin Dow Limited, Plot 37, Sector 19,
Korangi Industrial Area, Karachi-74900, Pakistan

ہدایات:
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
روشنی، گرمی اور نمی سے محفوظ رکھیں۔
۳۰°C گرمی سے کم درجہ حرارت پر رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کی جائے۔

ATNAHS
Martin Dow