Bonviva®

Ibandronic acid sodium

Bisphosphonate – Drugs for treatment of bone diseases (M05)

PHARMACEUTICAL FORM

Bonviva 2.5mg film-coated tablets

Film-coated tablets of oblong shape and white to off white in color

QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: ibandronic acid, monosodium salt, monohydrate.

One film-coated tablet contains 2.813 mg of ibandronic acid, monosodium salt, monohydrate equivalent to 2.5 mg of ibandronic acid.

CLINICAL PARTICULAR

Therapeutic Indications

Bonviva is indicated for the treatment of postmenopausal osteoporosis, to reduce the risk of fractures and for the prevention of bone loss in postmenopausal women who are at risk of developing osteoporosis.

Treatment of Osteoporosis: Osteoporosis may be confirmed by the finding of low bone mass (T score < 2.0 SD) and/or by the presence or history of osteoporotic fracture.

Prevention of Osteoporosis: Bone loss is particularly rapid in postmenopausal women younger than age 60. Factors such as family history of osteoporosis, early menopause, previous fracture, high bone turnover, low bone mineral density (BMD) (at least 1.0 SD below the premenopausal mean), thin body frame, Caucasian or Asian race, and smoking, are associted with an increased risk of developing osteoporosis and fractures. The presence of these risk factors may be important when considering the use of Bonviva for preventing osteoporosis.

Dosage and Method of Administration

Standard Dosage

The recommended dose of Bonviva for treatment and prevention is one 2.5 mg film-coated tablet once daily.

Bonviva should be taken 60 minutes before the first foodor drink (other than water) of the day or any other oral medication or supplementation (including calcium):

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

Patients should receive supplemental calcium or vitamin D if dietary intake is inadequate.

Special Dosage Instructions

Patients with hepatic impairment

No dosage adjustment is necessary (see. Pharmacokinetics in Special Populations).

Patients with renal impairment

No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal or greater than 30 mL/min.

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

Elderly

No dosage adjusment is necessary.

Children

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

Contraindications

• Bonviva is contraindicated in patients with known hypersensitivity to Ibandronic acid or to any of the excipients.

• Uncorrected hypocalcemia.

• Inability to stand or sit upright for least 60 minutes.

Special Warning and Special Precaution for Use

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

Bisphosphonates have been associated with dysphagia, oesophagitis and oesophageal or gastric ulcers. Therefore, patients should pay particular attention and be able to comply with the dosing instructions (see Standard Dosage)

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

Since NSAIDs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant medication with Bonviva.

Interaction with other Medical Products and other Forms of interaction

Drug-Food Interactions

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

Drug-Drug Interaction

It is likely that calcium supplements, antacids and some oral medications containing multivalent cations (such as aluminium, magnesium, iron) are likely to interfere with the absorption of Bonviva. Therefore, patients must wait 60 minutes after taking Bonviva before taking other oral medications.

Pharmacokinetic interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen of 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, i.v. ranitidine caused an increase in Ibandronic acid bioavailability of about 20 %, probably as a result of reduced gastric acidity. However, since this increase is within the normal range of the bioavailability of Ibandronic acid, no dosage adjustment is required when Bonviva is administered with H2-antagonists or other drugs which increase gastric pH.

In relation to disposition, no drug interactions of clinical significance are considered likely, since Ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic 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.

Pregnancy and Lactation

Bonviva should not be used during pregnancy and lactation.

Pregnancy

There was no evidence for a direct fetal 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).

There is no clinical experience with Bonviva in pregnant women.

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 correponded to about 5 % of the concentration measured after 2 hours.

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

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed.

Undesirable Effects

Experience from Clinical Trial

Treatment of postmenopausal osteoporosis

Table 1 lists adverse events from the pivotal anti-fracture phase III trial MF 4411, reported as possibly or probably related to trial medication, in more than 1% of the patients treated with either Bonviva 2.5 mg daily or placebo.

Adverse drug reactions that are equally frequent in both active and placebo or more frequent in placebo-treated patients are excluded.

Table 1 : Related adverse drug reactions reported at a frequency of greater than 1 % and greater than placebo

Adverse drug reaction	Placebo N=975 patients ADR No. (%)	Bonviva 2.5 mg daily N=977 patients ADR No. (%)
Digestive system		
Dyspepsia	34 (3.5)	54 (5.5)

Diarrhea	14 (1.4)	21 (2.1)
Musculoskeletal system Myalgia	8 (0.8)	18 (1.8)
Skin and appendages Rash	7 (0.7)	12 (1.2)

Prevention of postmenopausal osteoporosis

The safety profile of Bonviva 2.5 mg daily from the prevention phase II/III trial MF 4499 (N=163 patients with Bonviva 2.5 mg, N=159 patients with placebo was compared for consistency against the safety data from the pivotal anti-fracture efficacy trial MF 4411 and does not bring any additional safety information.

Abnormal laboratory findings

There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, impaired hematologic system, hypocalcemia or hypophosphatemia.

Post Marketing Experience

There is no post-marketing experience with Bonviva. However, there is post-marketing experience with i.v. administration of Ibandronic acid. So far, no data were reported with the i.v. administration of 1 to 4 mg Ibandronic acid in the treatment of hypercalcemia of malignancy with regard to adverse drug reactions, which might add information to the oral administration of Bonviva.

Overdose

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

PHARMACOLOGICAL PROPERTIES & EFFECTS

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 mineralisation 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 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.

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

Following treatment discontinuation, there is a reversion to the pathological pre-treatment rates of elevated bone resorption associated with postmenopausal osteoporosis.

The histological analysis of bone biopsies after two and three years of treatment of postmenopausal women showed bone of normal quality and no indication of a mineralisation defect.

Mechanism of action

Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonate, which act on bone tissue and specifically inhibit osteoclast activity. It does not interfere with osteoclast recruitment. The selective action of Ibandronic acid on bone tissue is based on the high affinity of this compound for hydroxyapatite, which represents the mineral matrix of the bone.

Ibandronic acid reduces bone resorption, with no direct effect on bone formation. In postmenopausal women, it reduces the elevated rate of bone turnover towards premenopausal levels, leading to a progressive net gain in bone mass.

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

Efficacy / Clinical Studies

Treatment of postmenopausal osteoporosis

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 statiscally 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 fratures 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 statiscally 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 spesifically 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 (femonal neck BMD T-score <-3.0 SD). The observation of non-vertebral fractures efficacy in high-risk subgroups is consistent with clinical trial findings for other biophosphonates.

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.

Prevention of postmenopausal osteoporosis
Prevention of bone loss was demonstrated in a double blind, placebo-controlled study of 2-year duration with spine BMD change as the primary endpoint. This study compared daily Ibandronic acid at three dose levels (0.5 mg, 1.0 mg, 2.5 mg) with placebo. A calcium supplement of 500 mg daily was provided to each patient. The study enrolled 653 postmenopausal women without osteoporosis (648 were eligible for efficacy) stratified according to time since menopause (1-3 years, >3 years) and baseline lumbar spine BMD (T score:>-1, -1 to -2.5).

Bonviva 2.5 mg daily resulted in a mean increase in BMD of 3.1% compared with placebo and 1.9 % relative to baseline. In the placebo group, a BMD decrease of approximately 1% at the lumbar spine occurred over two years, confirming the known accelerated bone loss early after menopause. Irrespective of the time since menopause or the degree of pre-existing bone loss, treatment with Bonviva resulted in a statistically higher BMD response at the lumbar spine than placebo across all four strata. Seventy percent of the patients receiving Bonviva responded to treatment, response being defined as a lumbar spine BMD increase from baseline.

Bonviva also resulted in a significant mean BMD increase at the total hip by 1.8% compared to the placebo group (mean relative change from baseline of 1.2%).

A clinically meaningful reduction in biochemical markers of bone resorption (urinary CTX) was observed as early as one month after the start of treatment.

Pharmacokinetic properties

The pharmacological effects of ibandronic acid are not directly related to actual plasma concentrations. This was demonstrated by various studies in animals and in humans, in which equivalent efficacy of ibandronic acid was demonstrated following either daily or intermittent regimens, consisting of a drug-free interval of several weeks (at least 6 weeks in rats, at least 11 weeks in dogs, at least 30 days in monkeys, and at least 9.5 weeks in humans) provided the same total dose was administered over this period.

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. 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 ibandronic acid 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 a meal. Both bioavailability and BMD gains are reduced when food or beverage are taken less than 60 minutes after Bonviva.

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.

Metabolism

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

Elimination

The absorbed fraction of ibandronic acid is removed from the circulation via bone absorption (40-50%) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid is eliminated unchanged in the feces.

The range of observed apparent half-lives is broad and dependent on dose and assay sensitivity, but the apparent terminal half-life is generally in the range of 10-60 hours. However, 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 creatinin clearance. The difference between the apparent total and renal clearances is considered to reflect the uptake by bone.

Pharmacokinetics in Special Populations

Gender

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

Race
There is no evidence for clinically relevant interethnic differences between Asians and Caucasians in ibandronic acid disposition. There are few data avaiable 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 adjustmen is necessary for patients with mild or moderate renal impairment (CLcr ≥30mL/min).

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

Patients with hepatic impairment

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

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 fctor

to take into consideration (see chapter “Patients with renal impairment”, mentioned above).

Children

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

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.

No indication of carcinogenic and genotoxic potential has been observed.

Stability

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

Storage Conditions

Store below 30^0C **Packs**

Box, 1 bottle @ 28 film coated tablet

Medicine: Keep out of reach and sight of children On medical Prescription only Harus dengan resep dokter

Made by:

F. Hoffmann- La Roche Ltd, Basel, Switzerland

Imported by:

PT Roche Indonesia

Depok, Indonesia