**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Bonviva 150 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
Contains 154.6 mg anhydrous lactose (equivalent to 162.75 mg lactose monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

Posology
The recommended dose is one 150 mg film-coated tablet once a month. The tablet should preferably be taken on the same date each month.

Bonviva should be taken after an overnight fast (at least 6 hours) and 1 hour before the first food or drink (other than water) of the day (see section 4.5) or any other oral medicinal products or supplementation (including calcium).

In case a dose is missed, patients should be instructed to take one Bonviva 150 mg tablet the morning after the tablet is remembered, unless the time to the next scheduled dose is within 7 days.
Patients should then return to taking their dose once a month on their originally scheduled date.
If the next scheduled dose is within 7 days, patients should wait until their next dose and then continue taking one tablet once a month as originally scheduled.
Patients should not take two tablets within the same week.

Patients should receive supplemental calcium and / or vitamin D if dietary intake is inadequate (see section 4.4 and section 4.5).

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 benefits and potential risks of Bonviva on an individual patient basis, particularly after 5 or more years of use.

*Special populations*
*Patients with renal impairment*
Bonviva is not recommended for patients with a creatinine clearance below 30 ml/min due to limited clinical experience (see section 4.4 and section 5.2).
No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal or greater than 30 ml/min.

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

*Elderly population (>65 years)*
No dose adjustment is required (see section 5.2).

*Paediatric population*
There is no relevant use of Bonviva in children below 18 years, and Bonviva was not studied in this population. (see section 5.1 and section 5.2).

Method of administration
For oral use.

- Tablets should be swallowed whole with a glass of water (180 to 240 ml) while the patient is sitting or standing in an upright position. Water with a high concentration of calcium should not be used. If there is a concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.
- Patients should not lie down for 1 hour after taking Bonviva.
- Water is the only drink that should be taken with Bonviva.
- Patients should not chew or suck the tablet, because of a potential for oropharyngeal ulceration

## 4.3 Contraindications

- Hypersensitivity to ibandronic acid or to any of the excipients listed in section 6.1
- Hypocalcaemia
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 60 minutes

## 4.4 Special warnings and precautions for use

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

Gastrointestinal irritation
Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Bonviva is given to patients with active upper gastrointestinal problems (e.g. known Barrett's oesophagus, dysphagia, other oesophageal diseases, gastritis, duodenitis or ulcers).
Adverse reactions such as oesophagitis, oesophageal ulcers and oesophageal erosions, in some cases severe and requiring hospitalisation, rarely with bleeding or followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. The risk of severe oesophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction and/or who continue to take oral bisphosphonates after developing symptoms suggestive of oesophageal irritation. Patients should pay particular attention to and be able to comply with the dosing instructions (see section 4.2).

Physicians should be alert to any signs or symptoms signaling a possible oesophageal reaction and patients should be instructed to discontinue Bonviva and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.
While no increased risk was observed in controlled clinical trials there have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications.

Since Nonsteroidal Anti-Inflammatory medicinal products and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported very rarely in the post marketing setting in patients receiving Bonviva for osteoporosis (see section 4.8).

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth.

A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Bonviva in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:
- Potency of the medicinal product that inhibit bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Bonviva. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Bonviva administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of Bonviva treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. 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.

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.

Renal impairment
Due to limited clinical experience, Bonviva is not recommended for patients with a creatinine clearance below 30 ml/min (see section 5.2).

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

## 4.5 Interaction with other medicinal products and other forms of interaction

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

*Interactions with other medicinal products*
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). Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation.

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

Acetylsalicylic acid and NSAIDs
Since Acetylsalicylic acid, Nonsteroidal Anti-Inflammatory medicinal products (NSAIDs) and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration (see section 4.4).

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

In healthy male volunteers and postmenopausal women, intravenous administration of ranitidine caused an increase in ibandronic acid bioavailability of about 20 %, probably as a result of reduced gastric acidity. However, since this increase is within the normal variability of the bioavailability of ibandronic acid, no dose adjustment is considered necessary when Bonviva is administered with H2-antagonists or other active substances which increase gastric pH.

## 4.6 Fertility, pregnancy and lactation

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

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

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

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that Bonviva has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile
The most serious reported adverse reactions are anaphylactic reaction/shock, atypical fractures of the femur, osteonecrosis of the jaw, gastrointestinal irritation, ocular inflammation, (see paragraph "Description of selected adverse reactions" and section 4.4).
The most frequently reported adverse reactions are arthralgia and influenza-like symptoms. These symptoms are typically in association with the first dose, generally of short duration, mild or moderate in intensity, and usually resolve during continuing treatment without requiring remedial measures (see paragraph "Influenza like illness").

Tabulated list of adverse reactions
In table 1 a complete list of known adverse reactions is presented. The safety of oral treatment with ibandronic acid 2.5 mg daily was evaluated in 1251 patients treated in 4 placebo-controlled clinical studies, with the large majority of patients coming from the pivotal three year fracture study (MF4411).

In a two-year study in postmenopausal women with osteoporosis (BM 16549) the overall safety of Bonviva 150 mg once monthly and ibandronic acid 2.5 mg daily was similar. The overall proportion of patients who experienced an adverse reaction, was 22.7 % and 25.0 % for Bonviva 150 mg once monthly after one and two years, respectively. Most cases did not lead to cessation of therapy.

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000),very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions occurring in postmenopausal women receiving Bonviva 150 mg once monthly or ibandronic acid 2.5 mg daily in the phase III studies BM16549 and MF4411 and in post-marketing experience.

| **System Organ Class** | **Common** | **Uncommon** | **Rare** | **Very rare** |
|---|---|---|---|---|
| Immune system disorders | | Asthma exacerbation | Hypersensitivity reaction | Anaphylactic reaction/shock*† |
| Metabolism and nutrition disorders | | hypocalcaemia | | |
| Nervous system disorders | Headache | Dizziness | | |
| Eye disorders | | | Ocular inflammation*† | |
| Gastrointestinal disorders* | Oesophagitis, Gastritis, Gastro oesophageal reflux disease, Dyspepsia, Diarrhoea, Abdominal pain, Nausea | Oesophagitis including oesophageal ulcerations or strictures and dysphagia, Vomiting, Flatulence | Duodenitis | |
| Skin and subcutaneous tissues disorders | Rash | | Angioedema, Face oedema, Urticaria | Stevens-Johnson Syndrome†, Erythema Multiforme†, Dermatitis Bullous† |
| Musculoskeletal and connective tissue disorders | Arthralgia, Myalgia, Musculoskeletal pain, Muscle cramp, Musculoskeletal stiffness | Back pain | Atypical subtrochanteric and diaphyseal femoral fractures† | Osteonecrosis of jaw*† Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)† |
| General disorders and administration site conditions | Influenza like illness* | Fatigue | | |

*See further information below
†Identified in post-marketing experience.

Description of selected adverse reactions

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

*Influenza-like illness*
Influenza-like illness includes events reported as acute phase reaction or symptoms including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, or bone pain.

*Osteonecrosis of jaw*
Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as ibandronic acid (see section 4.4.) Cases of ONJ have been reported in the post marketing setting for ibandronic acid.

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

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

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products for treatment of bone diseases, bisphosphonates, ATC code: M05-BA06

*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. 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.

*Pharmacodynamic effects*
The pharmacodynamic action of ibandronic acid is inhibition of bone resorption. *In vivo*, ibandronic acid prevents experimentally induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. In young (fast growing) rats, the endogenous bone resorption is also inhibited, leading to increased normal bone mass compared with untreated animals.
Animal models confirm that ibandronic acid is a highly potent inhibitor of osteoclastic activity. In growing rats, there was no evidence of impaired mineralization even at doses greater than 5,000 times the dose required for osteoporosis treatment.
Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys was associated with formation of 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 ibandronic acid demonstrated anti-fracture efficacy.

In animal models ibandronic acid produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including suppression of urinary biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked N-telopeptides of type I collagen (NTX)).

In a Phase 1 bioequivalence study conducted in 72 postmenopausal women receiving 150 mg orally every 28 days for a total of four doses, inhibition in serum CTX following the first dose was seen as early as 24 hours post-dose (median inhibition 28 %), with median maximal inhibition (69 %) seen 6 days later. Following the third and fourth dose, the median maximum inhibition 6 days post dose was 74 % with reduction to a median inhibition of 56 % seen 28 days following the fourth dose. With no further dosing, there is a loss of suppression of biochemical markers of bone resorption.

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

Bonviva 150 mg once monthly

Bone mineral density (BMD)
Bonviva 150 mg once monthly was shown to be at least as effective as ibandronic acid 2.5 mg daily at increasing BMD in a two year, double-blind, multicentre study (BM 16549) of postmenopausal women with osteoporosis (lumbar spine BMD T score below -2.5 SD at baseline). This was demonstrated in both the primary analysis at one year and in the confirmatory analysis at two years endpoint (Table 2).

Table 2: Mean relative change from baseline of lumbar spine, total hip, femoral neck and trochanter BMD after one year (primary analysis) and two years of treatment (Per-Protocol Population) in study BM 16549.

| | One year data in study BM 16549 | | Two year data in study BM 16549 | |
|---|---|---|---|---|
| Mean relative changes from baseline % [95% CI] | ibandronic acid 2.5 mg daily (N=318) | Bonviva 150 mg once monthly (N=320) | ibandronic acid 2.5 mg daily (N=294) | Bonviva 150 mg once monthly (N=291) |
| Lumbar spine L2-L4 BMD | 3.9 [3.4, 4.3] | 4.9 [4.4, 5.3] | 5.0 [4.4, 5.5] | 6.6 [6.0, 7.1] |
| Total hip BMD | 2.0 [1.7, 2.3] | 3.1 [2.8, 3.4] | 2.5 [2.1, 2.9] | 4.2 [3.8, 4.5] |
| Femoral neck BMD | 1.7 [1.3, 2.1] | 2.2 [1.9, 2.6] | 1.9 [1.4, 2.4] | 3.1 [2.7, 3.6] |
| Trochanter BMD | 3.2 [2.8, 3.7] | 4.6 [4.2, 5.1] | 4.0 [3.5, 4.5] | 6.2 [5.7, 6.7] |

Furthermore, Bonviva 150 mg once monthly was proven superior to ibandronic acid 2.5 mg daily for increases in lumbar spine BMD in a prospectively planned analysis at one year, $p=0.002$, and at two years, $p<0.001$.

At one year (primary analysis), 91.3 % ($p=0.005$) of patients receiving Bonviva 150 mg once monthly had a lumbar spine BMD increase above or equal to baseline (BMD responders), compared with 84.0 % of patients receiving ibandronic acid 2.5 mg daily. At two years, 93.5 % ($p=0.004$) and 86.4 % of patients receiving Bonviva 150 mg once monthly or ibandronic acid 2.5 mg daily, respectively, were responders.

For total hip BMD, 90.0 % ($p<0.001$) of patients receiving Bonviva 150 mg once monthly and 76.7 % of patients receiving ibandronic acid 2.5 mg daily had total hip BMD increases above or equal to baseline at one year. At two years 93.4 % ($p<0.001$) of patients receiving Bonviva 150 mg once

monthly and 78.4 %, of patients receiving ibandronic acid 2.5 mg daily had total hip BMD increases above or equal to baseline.

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

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

At one year, 83.5 % ($p= 0.006$) of patients receiving Bonviva 150 mg once monthly and 73.9 % of patients receiving ibandronic acid 2.5 mg daily were identified as responders (defined as a decrease ≥50 % from baseline). At two years 78.7 % ($p=0.002$) and 65.6 % of patients were identified as responders in the 150 mg monthly and 2.5 mg daily arms respectively.

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

Ibandronic acid 2.5 mg daily

In the initial three-year, randomised, double-blind, placebo-controlled, fracture study (MF 4411), a statistically significant and medically relevant decrease in the incidence of new radiographic morphometric and clinical vertebral fractures was demonstrated (table 3). In this study, ibandronic acid was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently as an exploratory regimen. Ibandronic acid was taken 60 minutes before the first food or drink of the day (post-dose fasting period). The study enrolled women aged 55 to 80 years, who were at least 5 years postmenopausal, who had a BMD at lumbar spine of 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral fractures. All patients received 500 mg calcium and 400 IU vitamin D daily. Efficacy was evaluated in 2,928 patients. ibandronic acid 2.5 mg administered daily, showed a statistically significant and medically relevant reduction in the incidence of new vertebral fractures. This regimen reduced the occurrence of new radiographic vertebral fractures by 62 % ($p=0.0001$) over the three year duration of the study. A relative risk reduction of 61 % was observed after 2 years ($p=0.0006$). No statistically significant difference was attained after 1 year of treatment ($p=0.056$). The anti-fracture effect was consistent over the duration of the study. There was no indication of a waning of the effect over time.
The incidence of clinical vertebral fractures was also significantly reduced by 49 % ($p=0.011$). The strong effect on vertebral fractures was furthermore reflected by a statistically significant reduction of height loss compared to placebo ($p<0.0001$).

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

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

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

Table 4: 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) | ibandronic acid 2.5 mg daily (N=575) |
|---|---|---|
| Relative Risk Reduction New morphometric vertebral fractures | | 59 % (34.5, 74.3) |
| Incidence of new morphometric vertebral fractures | 12.54 % (9.53, 15.55) | 5.36 % (3.31, 7.41) |
| Relative risk reduction of clinical vertebral fracture | | 50 % (9.49, 71.91) |
| Incidence of clinical vertebral fracture | 6.97 % (4.67, 9.27) | 3.57 % (1.89, 5.24) |
| BMD – mean change relative to baseline lumbar spine at year 3 | 1.13 % (0.6, 1.7) | 7.01 % (6.5, 7.6) |
| BMD – mean change relative to baseline total hip at year 3 | -0.70 % (-1.1, -0.2) | 3.59 % (3.1, 4.1) |

In the overall patient population of the study MF4411, no reduction was observed for non-vertebral fractures, however daily ibandronic acid appeared to be effective in a high-risk subpopulation (femoral neck BMD T-score < -3.0), where a non-vertebral fracture risk reduction of 69% was observed.

Daily treatment with 2.5 mg resulted in progressive increases in BMD at vertebral and nonvertebral sites of the skeleton.

Three-year lumbar spine BMD increase compared to placebo was 5.3 % and 6.5 % compared to baseline. Increases at the hip compared to baseline were 2.8 % at the femoral neck, 3.4 % at the total hip, and 5.5 % at the trochanter.
Biochemical markers of bone turnover (such as urinary CTX and serum Osteocalcin) showed the expected pattern of suppression to premenopausal levels and reached maximum suppression within a period of 3-6 months.
A clinically meaningful reduction of 50 % of biochemical markers of bone resorption was observed as early as one month after start of treatment with ibandronic acid 2.5 mg.

Following treatment discontinuation, there is a reversion to the pathological pre-treatment rates of elevated bone resorption associated with postmenopausal osteoporosis.
The histological analysis of bone biopsies after two and three years of treatment of postmenopausal women showed bone of normal quality and no indication of a mineralization defect.

*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 on bone are not directly related to actual plasma concentrations, as demonstrated by various studies in animals and humans.

*Absorption*
The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration and plasma concentrations increase in a dose-proportional manner up to 50 mg oral intake, with greater than dose-proportional increases seen above this dose. Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6 %. The extent of absorption is impaired when taken together with food or beverages (other than 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 the first food of the day. Both bioavailability and BMD gains are reduced when food or beverage is taken less than 60 minutes after ibandronic acid is ingested.

*Distribution*
After initial systemic exposure, ibandronic acid rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 l and the amount of dose reaching the bone is estimated to be 40-50 % of the circulating dose. Protein binding in human plasma is approximately 85 % - 87 % (determined *in vitro* at therapeutic concentrations), and thus there is a low potential for interaction with other medicinal products due to displacement.

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

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

The range of observed apparent half-lives is broad, the apparent terminal half-life is generally in the range of 10-72 hours. As the values calculated are largely a function of the duration of study, the dose used, and assay sensitivity, the true terminal half-life is likely to be substantially longer, in common with other bisphosphonates. Early plasma levels fall quickly reaching 10 % of peak values within 3 and 8 hours after intravenous or oral administration respectively.
Total clearance of ibandronic acid is low with average values in the range 84-160 ml/min. Renal clearance (about 60 mL/min in healthy postmenopausal females) accounts for 50-60 % of total clearance and is related to creatinine clearance. The difference between the apparent total and renal 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. 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*
Bioavailability and pharmacokinetics of ibandronic acid are similar in men and women.

*Race*
There is no evidence for any clinically relevant inter-ethnic differences between Asians and Caucasians in ibandronic acid disposition. There 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.
No dose adjustment is necessary for patients with mild or moderate renal impairment (CLcr equal or greater than 30 ml/min), as shown in study BM 16549 where the majority of patients had mild to moderate renal impairment.
Subjects with severe renal failure (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, total, renal, and non-renal clearances decreased by 67 %, 77 % and 50 %, respectively, in subjects with severe renal failure but there was no reduction in tolerability associated with the increase in exposure. Due to the limited clinical experience, Bonviva is not recommended in patients with severe renal impairment (see section 4.2 and section 4.4). The pharmacokinetics of ibandronic acid was not assessed in patients with end-stage renal disease managed by other than hemodialysis. The pharmacokinetics of ibandronic acid in these patients is unknown, and ibandronic acid should not be used under these circumstances.

*Patients with hepatic impairment (see section 4.2)*
There 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 dose adjustment is not necessary in patients with hepatic impairment.

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

*Paediatric population (see section 4.2 and section 5.1)*
There are no data on the use of Bonviva in these age groups.

## 5.3 Preclinical safety data

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

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

*Reproductive toxicity:*
There was no evidence for a direct foetal toxic or teratogenic effect of ibandronic acid in orally treated rats and rabbits and there were no adverse effects on the development in $F_1$ offspring in rats at an extrapolated exposure of at least 35 times above human exposure. 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 at 1.2 mg/kg/day. 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).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core*
Lactose monohydrate
Povidone
Cellulose, microcrystalline
Crospovidone
Stearic acid
Silica, colloidal anhydrous

*Tablet coat*
Hypromellose
Titanium dioxide (E 171)
Talc
Macrogol 6,000

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

5 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC, sealed with aluminium foil) containing 1 or 3 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. The release of pharmaceuticals in the environment should be minimized.

## 7. MARKETING AUTHORISATION HOLDER

Atnahs Pharma Netherlands B.V.
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/265/003
EU/1/03/265/004

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 2004
Date of latest renewal: 18 December 2013

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

## 1. NAME OF THE MEDICINAL PRODUCT

Bonviva 3 mg solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe of 3 ml solution contains 3 mg ibandronic acid (as sodium monohydrate).
The concentration of ibandronic acid in the solution for injection is 1mg per ml.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.
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.

### 4.2 Posology and method of administration

Patients treated with Bonviva should be given the package leaflet and the patient reminder card.

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

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.

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 benefits and potential risks of Bonviva on an individual patient basis, particularly after 5 or more years of use.

*Special populations*
*Patients with renal impairment*
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).

No dose 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.

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

*Elderly population (>65 years)*
No dose adjustment is required (see section 5.2).

*Paediatric population*
There is no relevant use of Bonviva in children below 18 years, and Bonviva was not studied in this population (see section 5.1 and 5.2).

Method of administration
For intravenous use over 15 - 30 seconds, every three months.

Strict adherence to the intravenous administration route is required (see section 4.4).

## 4.3 Contraindications

- Hypersensitivity to ibandronic acid or to any of the excipients listed in section 6.1
- Hypocalcaemia

## 4.4 Special warnings and precautions for use

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

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.

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 reactions occur, immediately discontinue the injection and initiate appropriate treatment.

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).

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

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported very rarely in the post marketing setting in patients receiving Bonviva for osteoporosis (see section 4.8).

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth.

A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Bonviva in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:
- Potency of the medicinal product that inhibit bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Bonviva. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Bonviva administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of Bonviva treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. 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.

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

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). Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation.

## 4.6 Fertility, 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.

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

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

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that Bonviva has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile
The most serious reported adverse reactions are anaphylactic reaction/shock, atypical fractures of the femur, osteonecrosis for the jaw and ocular inflammation (see paragraph “Description of selected adverse reactions” and section 4.4).
The most frequently reported adverse reactions are arthralgia and influenza-like symptoms. These symptoms are typically in association with the first dose, generally of short duration, mild or moderate in intensity, and usually resolve during continuing treatment without requiring remedial measures (please see paragraph “Influenza like illness”).

Tabulated list of adverse reactions
In table 1 a complete list of known adverse reactions is presented.
The safety of oral treatment with ibandronic acid 2.5 mg daily was evaluated in 1251 patients treated in 4 placebo-controlled clinical studies, with the large majority of patients coming from the pivotal three-year fracture study (MF 4411).

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 ibandronic acid 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 after one year and two years, respectively. Most cases of adverse reactions did not lead to cessation of therapy.

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions occurring in postmenopausal women receiving Bonviva 3 mg injection every 3 months or ibandronic acid 2.5 mg daily in the phase III studies BM16550 and MF 4411, and in post-marketing experience.

| **System Organ Class** | **Common** | **Uncommon** | **Rare** | **Very rare** |
|---|---|---|---|---|
| Immune system disorders | | Asthma exacerbation | Hypersensitivity reaction | Anaphylactic reaction/shock*† |
| Metabolism and nutrition disorders | | hypocalcaemia | | |
| Nervous system disorders | Headache | | | |
| Eye disorders | | | Ocular inflammation*† | |
| Vascular disorders | | Phlebitis/ thrombophlebitis | | |
| Gastrointestinal disorders | Gastritis, Dyspepsia, Diarrhoea, Abdominal pain, Nausea, Constipation | | | |
| Skin and subcutaneous tissues disorders | Rash | | Angioedema, Facial swelling/oedema, Urticaria | Stevens-Johnson Syndrome†, Erythema Multiforme†, Dermatitis Bullous† |
| Musculoskeletal and , connective tissue disorders | Arthralgia, Myalgia, Musculoskeletal pain, Back pain | Bone pain | Atypical subtrochanteric and diaphyseal femoral fractures† | Osteonecrosis of jaw*† Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)† |
| General disorders and administration site conditions | Influenza like illness*, Fatigue | Injection site reactions, Asthenia | | |

*See further information below
†Identified in post-marketing experience.

Description of selected adverse reactions

*Influenza-like illness*
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.

*Osteonecrosis of the jaw*
Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as ibandronic acid (see section 4.4.) Cases of ONJ have been reported in the post marketing setting for ibandronic acid.

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

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

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 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: M05BA06

*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. 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.

*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 ibandronic acid 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 ibandronic acid 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 ibandronic acid 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 ibandronic acid 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). This was demonstrated in both the primary analysis at one year and in the confirmatory analysis at two years endpoint (Table 2).

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 2).

Table 2: 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] | ibandronic acid 2.5 mg daily (N=377) | Bonviva 3 mg injection every 3 months (N=365) | ibandronic acid 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 ibandronic acid 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 ibandronic acid 2.5 mg daily.

Ibandronic acid 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 3). In this study, ibandronic acid was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently as an exploratory regimen. Ibandronic acid 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. Ibandronic acid 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 3: Results from 3 years fracture study MF 4411 (%, 95 % CI)

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

The treatment effect of ibandronic acid 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 4). The vertebral fracture risk reduction was very consistent with that seen in the overall population.

Table 4: 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) | ibandronic acid 2.5 mg daily (N=575) |
|---|---|---|
| Relative Risk Reduction New morphometric vertebral fractures | | 59% (34.5, 74.3) |
| Incidence of new morphometric vertebral fractures | 12.54% (9.53, 15.55) | 5.36% (3.31, 7.41) |
| Relative risk reduction of clinical vertebral fracture | | 50% (9.49, 71.91) |
| Incidence of clinical vertebral fracture | 6.97% (4.67, 9.27) | 3.57% (1.89, 5.24) |
| BMD – mean change relative to baseline lumbar spine at year 3 | 1.13% (0.6, 1.7) | 7.01% (6.5, 7.6) |
| BMD – mean change relative to baseline total hip at year 3 | -0.70% (-1.1, -0.2) | 3.59% (3.1, 4.1) |

In the overall patient population of the study MF4411, no reduction was observed for non-vertebral fractures, however daily ibandronic acid appeared to be effective in a high-risk subpopulation (femoral neck BMD T-score < -3.0), where a non-vertebral fracture risk reduction of 69% was observed.

Daily oral treatment with ibandronic acid 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 ibandronic acid daily.

A clinically meaningful reduction of 50 % of biochemical markers of bone resorption was observed as early as one month after starting treatment with ibandronic acid 2.5 mg.

*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 on bone are not directly related to actual plasma concentrations, as demonstrated by various studies in animals and humans.

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 interaction with other medicinal products due to displacement.

*Biotransformation*
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.

<u>Pharmacokinetics in special clinical situations</u>

*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 dose 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 dose adjustment is not necessary in patients with hepatic impairment.

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

*Paediatric population (see section 4.2 and section 5.1)*
There are no data on the use of Bonviva in these age groups.

## 5.3 Preclinical safety data

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

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

*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 $F_1$ 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 at 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 Shelf life

2 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 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.

### 6.6 Special precautions for disposal

Where the medicinal 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.

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.

## 7. MARKETING AUTHORISATION HOLDER

Atnahs Pharma Netherlands B.V.
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/265/005
EU/1/03/265/006

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 2004
Date of latest renewal: 18 December 2013

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Film-coated tablet:

IL CSM Clinical Supplies Management GmbH
Marie-Curie-Strasse 8
Lörrach
Baden-Württemberg
79539, Germany

Atnahs Pharma Denmark ApS,
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

Solution for injection in pre-filled syringe:

Atnahs Pharma Denmark ApS,
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minisation) milestone being reached.

**Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.

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**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Bonviva 150 mg film-coated tablets
Ibandronic acid

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

The tablets also contain lactose. See the package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
1 film-coated tablet
3 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not suck, chew or crush tablets
Read the package leaflet before use
Once monthly tablet
Oral use

Month 1 __/__/__ 3 film-coated tablets
Month 2 __/__/__ 3 film-coated tablets
Month 3 __/__/__ 3 film-coated tablets
Note down the date you take your tablet

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Atnahs Pharma Netherlands B.V.
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/265/003 1 film-coated tablet
EU/1/03/265/004 3 film-coated tablets

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Bonviva 150 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister foil**

## 1. NAME OF THE MEDICINAL PRODUCT

Bonviva 150 mg film-coated tablets
Ibandronic acid

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Atnahs Pharma Netherlands B.V.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Bonviva 3 mg solution for injection
Ibandronic acid

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe of 3 ml solution contains 3 mg of ibandronic acid (as sodium monohydrate).

## 3. LIST OF EXCIPIENTS

Also contains sodium chloride, glacial acetic acid, sodium acetate trihydrate, water for injections. See the package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe + 1 injection needle
4 pre-filled syringes + 4 injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous use only

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Atnahs Pharma Netherlands B.V.
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/265/005 1 pre-filled syringe
EU/1/03/265/006 4 pre-filled syringes

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

[Justification for not including Braille accepted]

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PRE-FILLED SYRINGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bonviva 3 mg solution for injection
Ibandronic acid
For IV use only

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mg/3 ml

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Bonviva**
150 mg film-coated tablets
Ibandronic acid

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**:


## 1. What Bonviva is and what it is used for

Bonviva belongs to a group of medicines called bisphosphonates. It contains the active substance ibandronic acid. Bonviva may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who take it, even though they won't be able to see or feel a difference. Bonviva may help lower the chances of breaking bones (fractures). This reduction in fractures was shown for the spine but not for the hip.

**Bonviva is prescribed to you to treat postmenopausal osteoporosis because you have an increased risk of fractures**. Osteoporosis is a thinning and weakening of the bones, which is common in women after the menopause. At the menopause, a woman's ovaries stop producing the female hormone, oestrogen, which helps to keep her skeleton healthy.

The earlier a woman reaches the menopause, the greater her risk of fractures in osteoporosis.

Other things that can increase the risk of fractures include:
- not enough calcium and vitamin D in the diet
- smoking, or drinking too much alcohol
- not enough walking or other weight-bearing exercise
- a family history of osteoporosis.

**A healthy lifestyle** will also help you to get the most benefit from your treatment. This includes:
- eating a balanced diet rich in calcium and vitamin D
- walking or any other weight-bearing exercise
- not smoking; and not drinking too much alcohol.

## 2. What you need to know before you take Bonviva

**Do not take Bonviva**
- If you are allergic to ibandronic acid, or any of the other ingredients of this medicine listed in section 6.
- If you have certain problems with your gullet/food pipe (oesophagus) such as narrowing or difficulty swallowing.
- If you can't stand or sit upright for at least one hour (60 minutes) at a time.
- **If you have, or had in the past low blood calcium**. Please consult your doctor.

**Warnings and precautions**
A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported very rarely in the post marketing setting in patients receiving Bonviva for osteoporosis. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Before receiving treatment, tell your doctor/nurse (health care professional) if:
- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction
- you don't receive routine dental care or have not had a dental check up for a long time
- you are a smoker (as this may increase the risk of dental problems)
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders)
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- you have cancer.

Your doctor may ask you to undergo a dental examination before starting treatment with Bonviva.

While being treated, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Bonviva.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Some people need to be especially careful while they're taking Bonviva. Talk to your doctor before taking Bonviva:
- If you have any disturbances of mineral metabolism (such as vitamin D deficiency).
- If your kidneys are not functioning normally.
- If you have any swallowing or digestive problems.

Irritation, inflammation or ulceration of the gullet/food pipe (oesophagus) often with symptoms of severe pain in the chest, severe pain after swallowing food and/or drink, severe nausea, or vomiting may occur, especially if you do not drink a full glass of water and/or if you lie down within an hour of taking Bonviva. If you develop these symptoms, stop taking Bonviva and tell your doctor straight away (see section 3).

**Children and adolescents**
Do not give Bonviva to children or adolescents below 18 years.

**Other medicines and Bonviva**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Especially:

- **Supplements containing calcium, magnesium, iron or aluminium**, as they could possibly influence the effects of Bonviva.

- Acetylsalicylic acid and other non-steroidal anti-inflammatory medicines (NSAIDs) (including ibuprofen, diclofenac sodium and naproxen) may irritate the stomach and intestine. Bonviva may also do so. So be especially careful if you take painkillers or anti-inflammatories while you're taking Bonviva.

After swallowing your monthly Bonviva tablet, **wait for 1 hour before taking any other medication**, including indigestion tablets, calcium supplements, or vitamins.

**Bonviva with food and drink:**
**Do not take Bonviva with food.** Bonviva is less effective if it's taken with food.
**You can drink water but no other drinks**

After you have taken Bonviva, please wait for 1 hour before you can have your first food and further drinks. (see 3. How to take Bonviva).

**Pregnancy and breast feeding**
Bonviva is for use only by postmenopausal women and must not be taken by women who could still have a baby.
Do not take Bonviva if you are pregnant or breast feeding.
Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**
You can drive and use machines as it's expected that Bonviva has no or negligible effect on your ability to drive and use machines.

**Bonviva contains lactose.**
If you have been told by your doctor that you cannot tolerate or digest some sugars (e.g. if you have a galactose intolerance, the Lapp lactase deficiency or have problems with glucose-galactose absorption), talk to your doctor before taking this medicine.

## 3. How to take Bonviva

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

**The usual dose of Bonviva is one tablet once a month**.

**Taking your monthly tablet**
It's important to follow these instructions carefully. They are designed to help your Bonviva tablet reach your stomach quickly, so it's less likely to cause irritation.

- **Take one Bonviva 150 mg tablet once a month**.
- **Choose one day of the month** that will be easy to remember. You can choose either the same date (such as the 1st of each month) or the same day (such as the first Sunday of each month) to take your Bonviva tablet. Choose the date that best fits your routine.
- Take your Bonviva tablet **at least 6 hours after you last had anything** to eat or drink except water.

- Take your Bonviva tablet
  - **after you first get up for the day**, and
  - **before you have anything to eat or drink** (on an empty stomach).

- **Swallow your tablet with a full glass of water** (at least 180 ml).

**Do not** take your tablet with water with a high concentration of calcium, fruit juice or any other drinks. If there is a concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.

- **Swallow your tablet whole**, do not chew it, crush it or let it dissolve in your mouth.

- **For the next hour (60 minutes)** after you've taken your tablet
  - **do not lie down**; if you do not stay upright (standing or sitting), some of the medicine could leak back into your oesophagus

  - **do not eat anything**

  - **do not drink anything** (except water if you need it)
  - **do not take any other medicines.**

- After you've waited for an hour, you can have your first food and drink of the day. Once you've eaten, it's OK to lie down if you wish, and to take any other medication you need.

**Continuing to take Bonviva**
It's important to keep taking Bonviva every month, as long as your doctor prescribes it for you. After 5 years of using Bonviva, please consult with your doctor whether you should continue to take Bonviva.

**If you take more Bonviva than you should**
If you've taken more than one tablet by mistake, **drink a full glass of milk and talk to your doctor straight away**.

**Do not make yourself vomit, and do not lie down** — this could cause Bonviva to irritate your oesophagus.

**If you forget to take Bonviva**

- If you forget to take your tablet on the morning of your chosen day, **do not take a tablet later in the day**.
  Instead, consult your calendar and find out when your next scheduled dose is.

- **If you forgot to take your tablet on your chosen day and your next scheduled dose is only 1 to 7 days away…**

  **Never take two Bonviva tablets within the same week**. You should wait until the next scheduled dose is due and take it as normal; then, continue taking one tablet once a month on the scheduled days you've marked on your calendar.

- **If you forgot to take your tablet on your chosen day and your next scheduled dose is more than 7 days away…**
  You should take one tablet the next morning after the day you remember; then, continue taking one tablet once a month on the scheduled days you've marked on your calendar.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Talk to a nurse or a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment**:

**Uncommon** (may affect up to 1 in 100 people):
- severe pain in the chest, severe pain after swallowing food or drink, severe nausea, or vomiting, difficulty in swallowing. You may have a severe inflammation of your gullet/food pipe, possibly with sores or constriction of the gullet/food pipe.

**Rare (**may affect up to 1 in 1000 people):
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing
- persistent eye pain and inflammation
- new pain, weakness or discomfort in your thigh, hip or groin. You may have early signs of a possible unusual fracture of the thigh bone.

**Very rare (**may affect up to 1 in 10,000 people):
- pain or sore in your mouth or jaw. You may have early signs of severe jaw problems (necrosis (dead bone tissue) in the jaw bone)
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear
- serious, potentially life-threatening allergic reaction
- severe adverse skin reactions.

**Other possible side effects**

**Common** (may affect up to 1 in 10 people):
- headache
- heartburn, discomfort in swallowing, stomach or tummy pain (may be due to an inflammation of the stomach), indigestion, nausea, having diarrhoea (loose bowels)
- muscle cramps, stiffness of your joints and limbs
- flu-like symptoms, including fever, shaking and shivering, feeling of discomfort, bone pain and aching muscles and joints. Talk to a nurse or doctor if any effects become troublesome or last more than a couple of days
- rash.

**Uncommon** (may affect up to 1 in 100 people):
- dizziness
- flatulence (farting, feeling bloated)
- back pain
- feeling tired and exhausted

- asthma attacks
- symptoms of low blood calcium levels (hypocalcaemia) including muscle cramps or spasms and/or tingling sensation in the fingers or around the mouth.

**Rare** (may affect up to 1 in 1000 people):
- inflammation of the duodenum (first section of the bowel) causing stomach pain
- hives.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Bonviva

Keep this medicine out of the sight and reach of children.

There are no special storage instructions.

Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Bonviva contains**

- The active substance is ibandronic acid. One tablet contains 150 mg of ibandronic acid (as sodium monohydrate).
- The other ingredients are:

**tablet core**: lactose monohydrate, povidone, cellulose microcrystalline, crospovidone, stearic acid purified, silica colloidal anhydrous

**tablet coat**: hypromellose, titanium dioxide (E 171), talc, macrogol 6000

**What Bonviva looks like and contents of the pack**

Bonviva tablets are white to off white, of oblong shape and marked "BNVA" on one side, and "150" on the other side. The tablets are supplied in blisters containing 1 or 3 tablets.
Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**
Atnahs Pharma Netherlands B.V.
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

**Manufacturer**

IL CSM Clinical Supplies Management GmbH
Marie-Curie-Strasse 8
Lörrach
Baden-Württemberg
79539, Germany

Atnahs Pharma Denmark ApS,
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

**This leaflet was last revised in .**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

**PLANNING WHEN TO TAKE BONVIVA**

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

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

It's important to keep taking Bonviva every month.

**Package leaflet: Information for the user**

**Bonviva 3 mg solution for injection**
ibandronic acid

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


## 1. What Bonviva is and what it is used for

Bonviva belongs to a group of medicines called bisphosphonates. It contains the active substance ibandronic acid.
Bonviva may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who take it, even though they won't be able to see or feel a difference. Bonviva may help lower the chances of breaking bones (fractures). This reduction in fractures was shown for the spine but not for the hip.

**Bonviva is prescribed to you to treat postmenopausal osteoporosis because you have an increased risk of fractures**. Osteoporosis is a thinning and weakening of the bones, which is common in women after the menopause. At the menopause, a woman's ovaries stop producing the female hormone, oestrogen, which helps to keep her skeleton healthy. The earlier a woman reaches the menopause, the greater her risk of fractures in osteoporosis.

Other things that can increase the risk of fractures include:
- not enough calcium and vitamin D in the diet
- smoking cigarettes, or drinking too much alcohol
- not enough walking or other weight-bearing exercise
- a family history of osteoporosis.

**A healthy lifestyle** will also help you to get the most benefit from your treatment. This includes:
- eating a balanced diet rich in calcium and vitamin D
- walking or other weight-bearing exercise
- not smoking and not drinking too much alcohol.

## 2. What you need to know before you receive Bonviva

**Do not receive Bonviva**
- **if you have, or had in the past, low blood calcium**. Please consult your doctor
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported very rarely in the post marketing setting in patients receiving Bonviva for osteoporosis. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Before receiving treatment, tell your doctor/nurse (health care professional) if:
- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction
- you don't receive routine dental care or have not had a dental check up for a long time
- you are a smoker (as this may increase the risk of dental problems)
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders)
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- you have cancer.

Your doctor may ask you to undergo a dental examination before starting treatment with Bonviva.

While being treated, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Bonviva.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Some patients need to be especially careful when using Bonviva. Talk to your doctor before receiving Bonviva:
- If you have or have ever had kidney problems, kidney failure or have needed dialysis, or if you have any other disease that may affect your kidneys
- If you have any disturbance of mineral metabolism (such as vitamin D deficiency)
- You should take calcium and vitamin-D supplements while receiving Bonviva. If you are unable to do so, you should inform your doctor
- If you have heart problems and the doctor recommended to limit your daily fluid intake.

Cases of serious, sometimes fatal allergic reaction have been reported in patients treated with intravenous ibandronic acid. If you experience one of the following symptoms, such as shortness of breath/difficulty breathing, tight feeling in throat, swelling of tongue, dizziness, feeling of loss of consciousness, redness or swelling of face, body rash, nausea and vomiting, you should immediately alert your doctor or nurse (see section 4).

**Children and adolescents**
Bonviva must not be used in children or adolescents below 18 years.

**Other medicines and Bonviva**
Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.

**Pregnancy and breast-feeding**
Bonviva is for use only by postmenopausal women and must not be taken by women who could still have a baby.
Do not take Bonviva if you are pregnant or breast-feeding.
Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**
You can drive and use machines as it's expected that Bonviva has no or negligible effect on your ability to drive and use machines.

**Bonviva contains less than 1 mmol sodium (23 mg) per dose (3 ml), i.e. essentially "sodium-free".**

## 3. How to receive Bonviva

The recommended dose of Bonviva for the intravenous injection is 3 mg (1 pre-filled syringe) once every 3 months.

The injection should be given into the vein by a physician or qualified/trained health care worker. Do not administer the injection to yourself.

The solution for injection must be administered into a vein only, and not anywhere else in the body.

**Continuing to receive Bonviva**
To get the most benefit from the treatment it is important to continue receiving the injections every 3 months for as long as your doctor prescribes it for you. Bonviva can treat osteoporosis only for as long as you keep receiving the treatment, even though you will not be able to see or feel a difference. After 5 years of receiving Bonviva, please consult with your doctor whether you should continue to receive Bonviva.

You should also take calcium and vitamin-D supplements, as recommended by your doctor.

**If too much Bonviva is given**
You may develop low levels of calcium, phosphorus or magnesium in the blood. Your doctor may take steps to correct such changes and may give you an injection containing these minerals.

**If a dose of Bonviva is missed**
You should arrange an appointment to get the next injection as soon as possible. After that, go back to getting the injections every 3 months from the date of the most recent injection.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Talk to a nurse or a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:**

**Rare (**may affect up to 1 in 1000 people):
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing
- persistent eye pain and inflammation (if prolonged)
- new pain, weakness or discomfort in your thigh, hip or groin. You may have early signs of a possible unusual fracture of the thigh bone.

**Very rare (**may affect up to 1 in 10000 people):
- pain or sore in your mouth or jaw. You may have early signs of severe jaw problems ( necrosis (dead bone tissue) in the jaw bone)
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear
- serious, potentially life-threatening allergic reaction (see section 2)
- severe adverse skin reactions.

**Other possible side effects**

**Common** (may affect up to 1 in 10 people):
- headache
- stomach pain (such as gastritis) or tummy pain, indigestion, nausea, having diarrhoea (loose bowels) or constipation
- pain in your muscles, joints, or back
- feeling tired and exhausted
- flu-like symptoms, including fever, shaking and shivering, feeling of discomfort, bone pain and aching muscles and joints. Talk to a nurse or doctor if any effects become troublesome or last more than a couple of days
- rash.

**Uncommon** (may affect up to 1 in 100 people)
- inflammation of a vein
- pain or injury at the injection site
- bone pain
- feeling weak
- asthma attacks
- symptoms of low blood calcium levels (hypocalcaemia) including muscle cramps or spasms and/or tingling sensation in the fingers or around the mouth.

**Rare** (may affect up to 1 in 1000 people):
- hives.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Bonviva

Keep this medicine out of the sight and reach of children.

This medicinal product does not require any special storage conditions.

Do not use Bonviva this medicine after the expiry date which is stated on the carton and on the syringe after "EXP". The expiry date refers to the last day of that month.

The person giving the injection should throw away any unused solution and put the used syringe and injection needle into an appropriate disposal container.

## 6. Content of the pack and other information

**What Bonviva contains**

- The active substance is ibandronic acid. One pre-filled syringe contains 3 mg of ibandronic acid in 3 ml of solution (as sodium monohydrate).
- The other ingredients are sodium chloride, acetic acid, sodium acetate trihydrate and water for injections.

**What Bonviva looks like and contents of the pack**

Bonviva 3 mg solution for injection in pre-filled syringes is a clear colourless solution. Each pre-filled syringe contains 3 ml of solution. Bonviva is available in 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.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**
Atnahs Pharma Netherlands B.V.
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

**Manufacturer**

Atnahs Pharma Denmark ApS,
Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S
Denmark

**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This information is intended for healthcare professionals only:

## INFORMATION FOR THE HEALTHCARE PROFESSIONALS

**Please see the Summary of Product Characteristics for more information.**

**Administration of Bonviva 3 mg solution for injection in pre-filled syringe:**

Bonviva 3 mg solution for injection in pre-filled syringe should be injected intravenously over a period of 15 - 30 seconds.

The solution is irritant, therefore strict adherence to the intravenous route of administration is important. If you inadvertently inject into the tissues around the vein, patients may experience local irritation, pain and inflammation at the injection site.

Bonviva 3 mg solution for injection in pre-filled syringe **must not** be mixed with calcium-containing solutions (such as Ringer-Lactate solution, calcium heparin) or other intravenously administered medicinal products. Where Bonviva is administered via an existing intravenous infusion line, the intravenous infusate should be restricted to either isotonic saline or 50 mg/ml (5 %) glucose solution.

**Missed dose:**
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.

**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, which can cause paraesthesia. In severe cases intravenous infusion of appropriate doses of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, may be needed.

**General advice:**
Bonviva 3 mg solution for injection in pre-filled syringe like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values.

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

Patients with concomitant diseases, or who use medicinal products which have a potential for undesirable effects on the kidney, should be reviewed regularly in line with good medical practice during treatment.

Any unused solution for injection, syringe and injection needle should be disposed of in accordance with local requirements.

# Annex IV

## Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

**Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for ibandronic acid, sodium ibandronate, the scientific conclusions of CHMP are as follows:

In view of available data on hypocalcaemia from spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and the fact that hypocalcaemia is an identified risk for ibandronic acid, the PRAC considers that a causal relationship between ibandronic acid and hypocalcaemia is established. The PRAC concluded that the product information of products containing ibandronic acid (osteoporotic indication (Bonviva)) should be amended accordingly.

Update of section 4.8 of the SmPC to add the ADR hypocalcaemia with a frequency uncommon. The Package leaflet is updated accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

**Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for ibandronic acid, sodium ibandronate the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing ibandronic acid, sodium ibandronate is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.