EU Risk Management Plan ibandronic acid/Bonviva/Bondronat

RMP version to be assessed as part of this application:

RMP Version number: 3.3 (4.0 on regulatory authority approval)

Data lock point for this RMP: 07 November 2023

Date of final sign-off: 17 November 2023

Rationale for submitting an updated RMP:

Updated as part of a type II safety variation for Bonviva (EMEA/H/C/0501/II/0074) and Bondronat (EMEA/H/C/0101/II/0089). The safety variation was triggered due to signal validation from a signal assessment report following a request from the Pharmaceuticals and Medical Devices Agency (PMDA), Japan to update the local product information to include atypical fractures at other sites than the femur. Subsequently updated as per Type II variation assessment report (EMEA/H/C/WS2451).

Summary of significant changes in this RMP:

The RMP was updated from Good Pharmacovigilance Practice (GVP) V – Risk Management Systems Revision 1 format to GVP V Rev. 2 format, and all applicable sections were updated in line with the revised template.

"Atypical fractures of the femur" was updated to "Atypical fractures of long bones" from an important potential risk to an important identified risk and further characterised.

Specific adverse drug reaction follow-up forms for osteonecrosis of the jaw and atypical fractures of the femur removed.

Routine Risk Minimisation Measures were updated in line with updated Summary of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs).

Part II Modules SI, SII, SIII, SIV.2, SIV.3 and SVII.1 updated in line with assessor's comments in the assessment report.

QPPV name: Jack O'Reilly

QPPV signature:

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Ibandronic acid
Pharmacotherapeutic group(s) (ATC Code)	Bisphosphonates (M05B A06)
Marketing Authorisation Applicant	Atnahs Pharma Netherlands B.V.
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Bonviva Bondronat
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Nitrogen-containing bisphosphonate containing active ingredient ibandronic acid (3-[N-methyl-N-pentyl] amino-1-hydroxypropane-1, 1- bisphosphonic acid), monosodium salt and monohydrate.
	Summary of mode of action: Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act on bone tissue and specifically inhibit osteoclast activity. It does not interfere with osteoclast recruitment. The selective action of ibandronate on bone tissue is based on the high affinity of this compound for hydroxyapatite, which represents the mineral matrix of the bone. Ibandronic acid reduces bone resorption, with no direct effect on bone formation. In postmenopausal women, it reduces the elevated rate of bone turnover towards premenopausal levels, leading to a progressive net gain in bone mass. Bone resorption due to malignant disease is characterised by excessive bone resorption not balanced with appropriate bone formation. Ibandronic acid selectively inhibits osteoclast activity reducing bone resorption and thereby reducing skeletal complications of the malignant disease.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	The production information including the SmPC and the PIL is included in Module 1.3.1 of the eCTD.

Indication(s) in the EEA	Bonviva is indicated for: • The treatment of osteoporosis in postmenopausal women at increased risk of fracture. A reduction in the risk of vertebral fracture has been demonstrated, efficacy on femoral neck fractures has not been established. Bondronat is indicated in adults for: • Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy of surgery) in patients with breast cancer and bone metastases. • Treatment of tumour-induced hypercalcaemia with or without metastases.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: **<u>Bonviva</u>** Bonviva is marketed in two strengths (150mg tablets and 3 mg solution for injection). <u>Bonviva 150mg film-coated tablets</u> 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. 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. <u>Bonviva 3mg solution for injection</u> 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. 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. **<u>Bondronat</u>** Bondronat is marketed in three strengths.

	Bondronat (2 mg and 6 mg solution for infusion) *Prevention of skeletal events in patients with breast cancer and bone metastases:* The recommended dose for prevention of skeletal events in patients with breast cancer and bone metastases is 6 mg IV injection given every 3-4 weeks. The dose should be infused over at least 15 minutes. *Treatment of tumour-induced hypercalcaemia:* In most patients with severe hypercalcemia (albumin-corrected serum calcium* ≥3 mmol/l or ≥12 mg/dl) 4 mg is an adequate single dose. In patients with moderate hypercalcemia (albumin-corrected serum calcium* ≥3 mmol/l or ≥12 mg/dl) 4 mg is an adequate single dose. In patients with moderate hypercalcemia (albumin-corrected serum calcium <3 mmol/L or < 12 mg/dL) 2 mg is an effective dose. 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. Bondronat concentrate for solution for infusion should be administered as an intravenous infusion over 2 hours. Bondronat (50mg tablets) The recommended dose is one 50 mg film-coated tablet daily. 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.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): **Bonviva** Bonviva 150 mg film-coated tablets Bonviva 3 mg solution for injection **Bondronat**

	Bondronat 2 mg concentrate for solution for infusion Bondronat 6 mg concentrate for solution for infusion Bondronat 50 mg film-coated tablets
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Bonviva

Indication: Osteoporosis in postmenopausal women at increased risk of fracture

Incidence:

Osteoporosis is the most common metabolic disorder of bone, affecting about 200 million people world-wide Sözen T *et al.* 2017. In the United States (US), it is estimated that 10 million people suffer from osteoporosis, of whom approximately 80% are females Wright NC *et al.* 2014.

Prevalence:

In Europe 1 in 3 women over 50 will be affected by osteoporosis. In the United Kingdom (UK), 21.9% of women aged 50 and older are estimated to have osteoporosis Willers C *et al.* 2022. The general prevalence of osteoporosis in the UK rises from 2% amongst women aged 50 years to 50% at 80 years National Institute for Health and Care Excellence (NICE). 2023. According to the World Health Organisation (WHO) diagnostic criteria for osteoporosis based on the measurement of bone mineral density (BMD), the prevalence of osteoporosis in the total Italian population amounted to 6.3% (approximately 4.5 million individuals) and increasing to over 50% in women over 50 Cipriani C *et al.* 2018. In Germany, amongst women aged 50 years and older, an estimated 39% have osteoporosis, with the prevalence rising from 23.3% (age 50-64 years) to 46.7% (age 65 to 74) and 59.2% (age 75 and over) Haussler B *et al.* 2007.

Demographics of the population in the authorized indication – age, gender, ethnic origin, and risk factors for the disease:

All patients treated for this indication are females, with 28% aged between 50-64, 33% aged between 65-74 39% aged ≥75 years old.

The main existing treatment options:
The main existing treatments for osteoporosis in postmenopausal women are summarised below Rosen HM 2023.

- Calcium: A daily intake of at least 1200 mg of calcium is recommended for all women with osteoporosis. Supplementation is usually required.
- Vitamin D: Recommended at 800 to 1000 IU daily for persons 50 years and older. Supplementation is usually required.
- Weight-bearing and muscle-strengthening exercise.
- Bisphosphonates: Bisphosphonates inhibit osteoclastic activity and are potent antiresorptive agents. Randomized clinical trials demonstrate a reduction of fractures with different bisphosphonates.
- Raloxifene: This selective estrogen receptor modulator is approved for the treatment of post-menopausal osteoporosis. Raloxifene has estrogen agonist activity on the bones and lipids, and an estrogen antagonist effect on the breast and uterus.
- Calcitonin: Calcitonin is an anti-resorptive agent approved for the treatment of post-menopausal osteoporosis. It is not considered first-line treatment for osteoporosis because more effective medications are available.
- Teriparatide: Recombinant human parathyroid hormone with potent bone anabolic activity. In a dosage of 20 µg per day given subcutaneously for up to two years, teriparatide decreases

vertebral and non-vertebral fractures.

- Denosumab: Human monoclonal antibody designed to inhibit receptor activator of nuclear factor kappa-B (RANK) ligand, a protein that acts as the primary signal for bone removal.
- Hormone therapy: Estrogen, with or without progesterone, slightly reduced the risk of hip and vertebral fractures, but this benefit must be pondered against the increased risk of vascular diseases and breast cancer, even for women at high risk of fractures.

Natural history of the indicated condition including mortality and morbidity:

Fractures are the clinical manifestation of osteoporosis and are a considerable economic burden. The most common fracture sites in osteoporosis and osteopenia patients are the hip, vertebrae, forearm, and upper humerus Warriner AH *et al.* 2011. Individuals who suffer osteoporotic fractures, particularly of their spine or hip, must deal with the complications, which include reductions in health- related quality-adjusted life years, increased morbidity and mortality Johnell O *et al.* 2004, Zhao DC *et al.* 2023.

Mortality in osteoporosis occurs most often as an indirect result of fracture and the complications of subsequent hospitalization. A Swedish study revealed high mortality after fractures with a 12-month mortality rate of 28% (after spine fractures), 22% (hip), 13% (shoulder), and 6% (forearm). The relative risk of mortality in 60-year-old women with fracture compared with those in the general population of the same age were 12.9 (spine), 10.4 (hip), 3.1 (shoulder) and 1.8 (forearm) Johnell O *et al.* 2004. A systematic review comparing mortality after hip fracture with a non-hip fracture control population revealed an excess mortality of between 8% and 36%. That is, for every 100 deaths in a non-hip fracture population over a period of 12 months, there would be (on average) between 108 and 136 deaths in a similar size population with hip fracture Abrahamsen *et al.* 2009.

Important co-morbidities:

Hypocalcaemia

Hypocalcaemia is an abnormal reduction in the serum ionized calcium concentration, and is defined as a serum calcium corrected level of <2.1 mmol/L. Hypocalcaemia is usually asymptomatic, but symptoms may include numbness or tingling sensations, especially in the area around the mouth, muscle spasms or muscle cramps. According to the Clinical Practice Guidelines from The National Kidney Foundation Disease Outcomes Quality Initiative (NKF KDOQI), clinical symptoms of hypocalcaemia include paraesthesia, Chvostek's sign, Rousseau's sign, caused by abnormalities in the production, secretion, or action of 1, 25-(OH)2 vitamin D because vitamin D facilitates calcium absorption through the small intestine. Vitamin D deficiency in-turn can be due to defects in the pathway of its synthesis and action Hall EJ *et al.* 2003, Golombick T *et al.* 2008, National Kidney Foundation. 2003.

Hypocalcaemia with increased bone turnover due to vitamin D deficiency is reported frequently in women treated for PMO. The prevalence of vitamin D deficiency among elderly women (mean age 83.7 years) living in residential homes has been estimated to be at least 50% National Kidney Foundation. 2003, Filcker L *et al.* 2003. Vitamin D deficiency is also associated with osteoporosis and osteofragility fractures, which result from a reduction in bone strength superimposed on trauma.

Postmenopausal women with hip fracture showed occult vitamin D deficiency. Calcium deficiency is insidious in its early stages and potentially irreversible in the latter, making preventative optimization the only successful pathway in all patients perceived to be at risk of calcium deficiency Golombick T *et al.* 2008.

Table SI.1: Epidemiology of Hypocalcemia in PMO when Unexposed to the Product

Identified Risk	Hypocalcemia		
Incidence and Prevalence	*Age Range [Year]*	*Incidence in Females per 1000 person years*	*Prevalence in Females*
	50-59	0.0	0.4%
	60-69	0.3	0.3%
	70-79	0.5	0.4%
	≥ 80	0.3	0.3%
Mortality of Condition	Not applicable		

All data presented are derived from UK GPRD. These are estimated age-related incidence and prevalence rates.

Renal disorder

The incidences of both osteoporosis and renal insufficiency increase with age therefore it is likely that many older women may have both renal insufficiency and PMO, Miller PD *et al.* 2005, Klawansky S *et al.* 2003.

Analysis of National Health and Nutrition Examination Survey (NHANES), 1988-1994 (NHANES III) data revealed that about 85% of women (aged from 20 to ≥ 80 years) with osteoporosis have mild to moderate renal insufficiency and 24% have severe renal compromise (GFR [glomerular filtration rate] <35 mL/min). In women with osteoporosis, the age specific prevalence for severe renal compromise is negligible through ages 50 to 59 and then rises steeply to about 54% for ages >80 years Klawansky S *et al.* 2003.

We used the UK GPRD data to estimate the prevalence and incidence of chronic kidney disease and acute renal failure in women with osteoporosis. Our analyses showed prevalence for these renal disorders to be 0.7% (ages 50 to 59), 0.92% (ages 60 to 69), 1.3% (ages 70 to 79), 2.1% (age ≥ 80). The corresponding incidence rates per 1000 person years were: 12.1 (ages 50 to 59), 25.6 (ages 60 to 69), 57.9 (ages 70 to 79), and 72.7 (age ≥80).

Annual mortality rates in the US vary from about 4.8% (GRF 3-44 ml/min) to 14% (GFR <15 ml/min) Go AS *et al.* 2004. Mortality amongst those on dialysis varies across Europe, with an annual incidence rate of 14% in France to 20% in the UK Rayner HC *et al.* 2004.

Table SI.2: Epidemiology of Renal Disorder in PMO when Unexposed to the Product

Potential Risk	Renal Disorder (Chronic kidney diseases and Acute Renal Failure)		
Incidence and Prevalence	*Age Range [Year]*	*Incidence in Females per 1000 person years*	*Prevalence in Females*
	50-59	3.2	0.7%
	60-69	10.3	0.9%
	70-79	36.9	1.3%
	≥ 80	46.8	2.1%
Mortality	Mortality rates for those on dialysis vary from 12-20% in European dialysis patients.		

CKD = Chronic Kidney Diseases

All data presented are derived from UK GPRD. These are estimated age-related incidence and prevalence rates.

Cardiovascular disease

Osteoporosis and cardiovascular disease are major causes of increased morbidity and mortality. Whilst historically viewed as separate disease entities that each increase in prevalence with aging, accumulating evidence indicates that in addition to sharing common risk factors (hypertension, non-insulin dependent diabetes mellitus [NIDDM), smoking, alcohol abuse and low physical activity) Anagnostis P *et al.* 2009 there are similar pathophysiological mechanisms underlying both McFarlane SI *et al.* 2004. There is an increasingly established relationship between osteoporosis and cardiovascular disease Sennerby U *et al.* 2007. Low bone mineral content at menopause is a risk factor for increased mortality in later life, especially from cardiovascular disease Anagnostis P *et al.* 2009. This could be in part because osteopenia is a marker for several factors which influence mortality.

The MORE study, a placebo-controlled study assessing the efficacy of raloxifene for the prevention of incident vertebral fractures in postmenopausal women, also investigated the impact of raloxifene treatment on the risk of cardiovascular disease Tankó LB *et al.* 2005. The study showed that women with osteoporosis had a 3.9-fold (95% confidence interval (CI), 2.0–7.7; $p < 0.001$) increased risk for cardiovascular events compared with women with low bone mass. A total hip BMD T score ≤ -2.5 versus a T score between -2.5 and -1 was associated with a 2.1-fold (95% CI, 1.2-3.6; $p < 0.01$) increase in risk, whereas presence of at least one vertebral fracture versus no vertebral fracture at baseline was associated with a 3.0-fold (95% CI, 1.8-5.1; $p < 0.001$) increase in risk.

The risk of cardiovascular events increased incrementally with the number and increasing severity of baseline vertebral fractures (both $p < 0.001$). Similarly, a study from Rotterdam revealed that, compared with women in the highest tertile for femoral neck BMD, those in the lowest tertile had a significantly increased risk of peripheral arterial disease (Odds Ratio (OR) = 1.49, 95% CI 1.16-1.91) van der Klift M *et al.* 2002. This is consistent with a systematic review and meta-analysis of the incidence of cardiovascular disease in longitudinal studies (study design), adjusted for potential confounders, between people with low BMD or fractures with people with higher BMD values or no fractures, which found that low BMD and fractures were associated with a modest increased risk of cardiovascular disease Veronese N *et al.* 2017. Similarly, a Norwegian study showed that decreased BMD (hazard ratio (HR) = = 1.41, 95% CI = 1.21-1.64) as well as osteoporosis of the femoral neck (HR = 2.05, 95% CI = 1.28-3.29) was independently associated with stroke and death Nordström A *et al.* 2010.

Pulmonary disease

Pulmonary disease is often co-morbid with osteoporosis Barr RG *et al.* 2009, Nuti R *et al.* 2009 and individuals with pulmonary disease such as chronic obstructive pulmonary disease are at increased risk of osteoporosis Gan WQ *et al.* 2004, Capsoni F. 2008.

A study conducted in California examining osteoporotic fractures in Women $\geq$ 65years, revealed that hip BMD loss was associated with increased mortality from pulmonary diseases (relative hazard = 1.6 per standard deviation (SD); 95% CI, 1.1-2.5) Kado DM *et al.* 2000.

A UK based cohort study conducted using the UK Clinical Practice Research Database (CPRD) showed that patients with asthma had a higher risk of osteoporosis (adjusted hazard ratio (aHR) 1.18, 95% CI 1.13–1.23) and were 12% (aHR 1.12, 95% CI 1.07–1.16) more likely to sustain fragility fractures than the general population Chalitsios CV *et al.* 2021. A high prevalence of fractures of 2.79 (95% CI: 1.19–6.54) in patients with steroid-dependent asthma was also reported in a cross-sectional study performed on 105 women with bronchial asthma Sosa M *et al.* 2006.

Non-insulin-dependent diabetes mellitus

There is also an established link between non-insulin-dependent diabetes mellitus (NIDDM) and osteoporosis. In the MORE trial women with osteoporosis had higher prevalence of NIDDM than women with low bone mass (2.6% vs 1.4%.) Tankó LB *et al.* 2005. Similarly studies in Norway, Sweden and the Netherlands have shown a 2 to 4 fold increased risk of hip fractures associated with Diabetes Ahmed LA *et al.* 2006, Holmberg AH *et al.* 2005, de Liefde II *et al.* 2005.

Table SI.3: Important Co-Morbidity in Target Population for Post Menopausal Osteoporosis

Co-Morbidity	**Epidemiological Information***		
Myocardial Infarction (MI)/ Unstable Angina	*Age Range [Years]*	*Incidence in Females*	*Prevalence in Females*
	50-59	1.3 of 1000	0.6%
	60-69	2.7 of 1000	2%
	70-79	5.6 of 1000	4%
	≥ 85	8.0 of 1000	6%
Stroke / Transient Ischemic Attack (TIA)	*Age Range [Years]*	*Incidence in Females*	*Prevalence in Females*
	50-59	1.4 of 1000	1%
	60-69	4.5 of 1000	3%
	70-79	12.3 of 1000	6%
	≥ 85	24.5 of 1000	11%
Type 2 Diabetes	*Age Range [Years]*	*Incidence in Females*	*Prevalence in Females*
	50-59	6.8 of 1000	2%
	60-69	10.8 of 1000	3.4%
	70-79	15.0 of 1000	5.3%
	≥ 85	11.7 of 1000	4.3%
Chronic Obstructive Pulmonary Diseases (COPD) / Chronic Obstructive Airways Diseases (COAD) / Asthma	*Age Range [Years]*	*Incidence in Females*	*Prevalence in Females*
	50-59	9.4 of 1000	15%
	60-69	13.6 of 1000	18%
	70-79	15.4 of 1000	19%
	≥ 85	11.3 of 1000	16%

COAD = Chronic Obstructive Airways Disease; COPD = Chronic Obstructive Pulmonary Disease; MI = Myocardial Infarction; TIA = Transient Ischemic Attack.

*All data presented are derived from UK GPRD in 2009. These are estimated age-related incidence and prevalence rates.

Bondronat

Indication: Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy of surgery) in patients with breast cancer and bone metastases

Incidence:

The skeleton is the most common site of metastatic cancer, and the breast is one of the most frequent sites of origin of bone metastases. Approximately 5% of patients present with distant metastases at their initial diagnosis of breast cancer, with bone being the most common site Jensen AØ et.al 2011. A retrospective review of 113,317 patients with bone metastases derived from the Surveillance, Epidemiology, and End Results (SEER) database reported an incidence of

bone metastases of 53.71% in breast cancer patients Huang *et al.* 2020.

Prevalence:

A Canadian retrospective cohort study (with long follow-up) of women diagnosed with early-stage breast cancer found that 13.6% of patients diagnosed in stage I-III will develop bone metastasis at 15 years of follow-up Liede A *et al.* 2016.

Demographics of the population in the authorized indication – age, gender, ethnic origin, and risk factors for the disease:

A Danish population-based cohort study reported a median age of 62.2 years (25-95 years) for diagnosis of bone metastases with breast cancer, and 67.4 years for those who subsequently developed skeletal-related events (e.g., pathological fractures, spinal cord compression, bone pain) Jensen AØ et.al 2011.

The main existing treatment options:
Traditionally the main treatment for bone metastases from breast cancer has been chemotherapy or endocrine therapy. Additional therapeutic options include pain management/analgesia, which may be administered in parallel with osteoclast inhibitors (such as bisphosphonates or denosumab), radiation therapy (external beam radiation therapy [EBRT], stereotactic body radiation therapy [SBRT] in one to five fractions), bone-targeting radiopharmaceuticals and surgery Yu & Hoffe 2022.

Natural history of the indicated condition including mortality and morbidity:

Breast cancer is mainly diagnosed in early stages (90–95%), however 20–30% of these patients become metastatic and to this day incurable. Bone is the single most frequent site for metastases and is involved in about 70% of all metastatic patients Manders K *et al.* 2006.

The 5-year relative survival rate for women with metastatic breast cancer in the U.S. is 30%. The 5-year survival rate for men with metastatic breast cancer is 19% Cancer.Net. 2023.

The median overall survival (OS) for bone-only metastatic breast cancer ranges from 40-65 months Ahn SG *et al.* 2013.

Important co-morbidities:

Comorbidities in patients with breast cancer is presented as a proxy for comorbidities in patients with metastatic bone disease. Data from eight US cancer care centers suggest that hypertension is the most common comorbidity among breast cancer patients (34.5%). The next most common conditions among breast cancer patients are: previous solid tumors (12.4%), diabetes (10.4%), respiratory disease (8.2%), psychiatric disease (5.8%), angina (4.2%), obesity (3.9%), myocardial infarction (3.1%), and stroke (2.8%) Barr RG *et al.* 2009. Age is associated with increased prevalence and severity of co- morbidities among cancer patients Piccirillo JF *et al.* 2008.

Hypocalcaemia

Hypocalcemia based on total calcium measurement is frequent in certain cancers (especially prostate) in association with osteosclerotic bone metastases. In a majority of these patients hypocalcemia is related to the low serum albumin and/or renal failure.

True ionized hypocalcemia may be seen as a toxic effect of certain chemotherapeutic agents or as a consequence of hyperphosphatemia due to rapid tumor lysis. In addition, tumors may produce osteoblast-stimulating factor(s) which cause massive accretion of calcium by the skeleton Ottewell PD. 2016.

In a series of inpatient oncologic cases with concomitant hypocalcaemia and bone metastasis, 7% of all breast cancer patients exhibited mild hypocalcaemia. None of those with breast cancer had severe hypocalcaemia; interestingly, most cases with severe hypocalcaemia had metastatic prostate cancer to the skeleton.

Hypocalcemia was found in 122 (1.6%) of the 7610 patients attending a large oncological center. In 10% of the cases, hypocalcemia was caused by hypoparathyroidism and/or uremia, in 12% it was related to a major infection. Osteoblastic metastases were responsible in 4% of the cases and in 74% hypocalcemia accompanied an impairment of the general condition due to the malignancy or its treatment, usually in the terminal stage of the disease. The most common cause of hypocalcemia in this group of patients seemed to be hypoproteinemia. Hypocalcemia thus seems to be a fairly common complication of malignant disease, the clinical relevance of which, however, appears to be relatively small in most cases Bolmqvist CP. 1986.

In a retrospective review of 143 patients with cancer and bone metastases Raskin P *et al.* 1973 observed hypocalcaemia in 16%. Prostate cancer accounted for the largest group of hypocalcaemic cancer patients. Similarly, a retrospective review of 7,063 adult cancer patients reported mild hypocalcaemia in 7% of all breast cancer patients (n=1198). None of those with breast cancer exhibited severe hypocalcaemia. Most cases with severe hypocalcaemia (5%) had metastatic prostate cancer to the skeleton Gonçalves JAF *et al.* 2019.

In another study of 112 patients with prostate cancer, 15 were discovered to be hypocalcaemic on the basis of serum total calcium measurement. Fourteen of these 15 patients had bone metastases. Serum total calcium, total protein, and albumin levels were significantly lower in patients with bone metastases (n = 61) than those without (n = 51). Hypocalcemia could be explained on the basis of hypoalbuminemia or renal failure in these patients. Plasma ionized Ca measurements were made in 47 of the total 112 patients. Only one patient with extensive bone metastases was found to be hypocalcaemic on the basis of ionized calcium measurement. Therefore, apparent hypocalcemia based on total calcium measurement is common in patients with prostate cancer (14% of all and 23% of those with bone metastases), whereas true hypocalcemia based on ionized calcium determinations is unusual Rutherford R. 2002.

One more recent study reported the association of hypocalcaemia and metastatic bone cancer of prostate in Italy. The study evaluated hypocalcaemia's prognostic role in a consecutive series of hormone-refractory bone metastatic patients with prostate cancer. The study measured serum calcium levels of the patients (n=192). There were 51 (26.6%) hypocalcaemic patients Tucci M *et al.* 2009.

No recent data were available on incidence, prevalence and mortality rates of hypocalcaemia in breast cancer patients.

Renal failure

The pathways leading to acute renal failure (ARF) in cancer patients are common to the development of ARF in other conditions. ARF may also develop due to aetiologies arising from cancer treatment or the disease itself, including nephrotoxic chemotherapy agents, post-renal obstruction, compression and infiltration, by malignancy, tumor lysis syndrome, uric acid, sepsis, and contrast agent nephropathy Lameire NH *et al.* 2005.

Renal impairment is a common comorbidity in cancer patients. It can delay excretion and alter metabolism of anticancer drugs leading to further renal toxicity. A Genentech study to be presented as the 2012 ASCO Annual Meeting was performed to determine the proportion of patients with renal impairment, including chronic kidney disease (CKD) and acute renal failure (ARF) after initiation of chemotherapy. The study included 1,896 lung cancer (LC), 1,088 colorectal cancer (CRC), 1,611

breast cancer chemotherapy- treated patients. The incidence of CKD ranged from 28.8% - 37.3%, and the incidence of ARF ranged from 11.8% - 24.8%.

Table SI.4: Epidemiology of Renal Disorder in Oncology when Unexposed to the Product

Potential Risk	Renal Disorder (Chronic kidney diseases[CKD] and Acute Renal Failure)
Incidence	CKD: 34.5% (Lung Cancer), 37.3% (Colorectal Cancer); 28.8% (Breast Cancer) ARF: 24.8% (Lung Cancer), 14.7% (Colorectal Cancer); 11.8% (Breast Cancer)

Atrial Fibrillation

Chronic non-cardiac diseases like cancer, chronic obstructive pulmonary disease (COPD), or chronic kidney disease might increase the risk of atrial fibrillation (AF) Lainscak M *et al.* 2008. Few data exist on AF and malignant diseases. In the study of Guzzetti, colon and breast cancer patients had threefold higher AF frequency compared to non-malignant patients Guzzetti S *et al.* 2008. AF risk was known to increase with excess inflammation Coussens LM *et al.* 2002.

Besides malignancy itself, increased inflammation might be an explanation for increased AF risk Chung MK *et al.* 2001, Guzzetti S *et al.* 2002. C-reactive protein values were found to be 1.5-fold higher in cancer patients Chung MK *et al.* 2001. AF was reported to be more frequent in patients with elevated postoperative neutrophil counts and, open colectomy patients with an excess inflammation compared to laparascopic surgery Wu FP *et al.* 2003, Siu CW *et al.* 2005.

Besides excess inflammation, cancer is a complex disease which alters hormonal, metabolic, autonomic nervous, hematologic, and especially coagulation systems and can interact with AF occurrence Rugo HS. 2004. Various cytostatics including anthracyclines, gemcitabine, melphalane, 5-fluorouracil, ifosfamide, cisplatin, docetaxel, etoposide, and higher doses of corticosteroids have cardiotoxic potential and might also induce AF van der Hooft CS *et al.* 2004, van der Hooft CS *et al.* 2006. Trastuzumab and lapatinib are anti- human epidermal growth factor receptor 2 (HER2) therapies known to have cardiotoxic potential and also may cause AF de Azambuja E *et al.* 2009.

The incidence of AF /flutter was 2.4% (192 of 7906) among cancer patients in the Danish Cancer Registry not exposed to IV bisphosphonates R Erichsen *et al.* 2011. Among elderly cancer patients included in a SEER-Medicare study, the 3-year incidence of AF in patients not exposed to IV bisphosphonates was 12.7% Wilkinson GS *et al.* 2010.

Indication: Treatment of tumor-induced hypercalcemia with or without metastases

Incidence:

Hypercalcemia occurs between 5% and 30% of cancer patients at some point during the course of the disease, depending on the type of tumor Lumachi F *et al.* 2009. Incidences ranging from 26%- 28% of lung cancer patients and 24%-26% of breast cancer patients have been reported Santarpia L *et al.* 2010.

Prevalence:

Based on a prevalence study, hypercalcemia of malignancy is reported in about 2 to 3% of patients with a cancer diagnosis, and it seems that it has been gradually decreasing over the years due to better treatment choices Bhandari S *et al.* 2019.

Demographics of the population in the authorized indication – age, gender, ethnic origin, and risk factors for the disease:

Hypercalcemia is most commonly observed as a complication in squamous cell carcinoma of the head, nick, lungs, breast, ovaries, kidneys as well as hematological malignancies like leukemia Vakiti *et al.* 2023.

The main existing treatment options:

Treatment of hypercalcemia of malignancy is aimed at lowering the serum calcium concentration by targeting the underlying disease, specifically by inhibiting bone resorption, increasing urinary calcium excretion, and to a lesser extent by decreasing intestinal calcium absorption. Because definitive serologic diagnosis takes several days, treatment is begun empirically at the time of presentation with adjustments occurring as laboratory information becomes available. The treatment options for hypercalcemia include IV hydration, calcitonin, corticosteroids, bisphosphonates, denosumab, gallium nitrate, prednisone, and hemodialysis Horowitz MJ 2022.

Natural history of the indicated condition including mortality and morbidity:

Cancer represents the most common etiology of hypercalcemia in the inpatient setting Linder G *et al.* 2013. The development of hypercalcemia is associated with poor prognosis, with 80% of patients dying within a year of diagnosis. Median survival is 3 to 4 months Seccareccia D. 2010.

Important co-morbidities:

In addition to the co-morbidities above for the indication of prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy of surgery) in patients with breast cancer and bone metastases, tumor-induced hypercalcemia is frequently reported with hypoalbuminemia, as 40% to 45% of the serum calcium is attached to albumin Vakiti *et al.* 2023.

Hypoalbuminemia

Hypoalbuminemia is often a finding on routine laboratory testing following the presentation of patients for other primary medical conditions or diseases. Patients with hypoalbuminemia present with peripheral (pitting) and central edema (ascites and effusions) and anasarca. They may also complain of fatigue and excessive weakness and other features of related nutritional deficiencies, for example, iron deficiency anemia in Celiac disease Vakiti *et al.* 2023.

Hyperparathyroidism

More than 90% of the cases of hypercalcemia are due to primary hyperparathyroidism and malignancy-induced hypercalcemia. Malignancy remains the most common cause of hypercalcemia in hospitalized patients Ramos REO *et al.* 2017. The increased secretion of parathyroid hormone-related peptide observed in hyperparathyroidism promotes bone resorption, increased phosphate excretion from the proximal tubules, and calcium reabsorption from the distal tubules in the kidney. Patients with hypercalcemia of malignancy tend to have advanced disease, and it portends a poor prognosis Ramos REO *et al.* 2017.

Part II: Module SII - Non-clinical part of the safety specification

SMPC INFORMATION

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 F1 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).

NON-CLINICAL PROGRAM OVERVIEW

The non-clinical program included acute, subchronic, chronic, reproductive toxicity, genotoxicity, and oral carcinogenicity studies, and local tolerance assays. This data concerns the use of ibandronic acid for both the PMO and the oncology indications. The *in vivo* studies were conducted with both oral and IV administration. A daily dosing regimen was used in all oral studies and IV studies up to 4 weeks. Intermittent dosing regimens were used in chronic IV studies. The safety of Bonviva 3 mg solution for injection with a 3 monthly dosing regimen and of Bonviva 150 mg tablets with a monthly dosing regimen are especially supported by the results of several single and intermittent IV dose studies in the rat and dog.

RENAL TOXICITY

The kidney was consistently identified as the primary target of systemic toxicity regardless of species and study design. However, there are published cases of renal failure in humans for other bisphosphonates Piccirillo JF *et al.* 2008. Therefore, the general testing strategy focused on the renal safety of the 3-monthly ibandronic acid regimen in humans. A dedicated toxicology program was conducted in the rat to examine the effects on specific structural targets within the kidney and their relationship to the dose levels, the dosing interval and the peak plasma concentrations Pfister T *et al.* 2007.

While published cases of renal failure seen with other bisphosphonates indicate at what doses these drugs potentially cause adverse renal effects, nephrotoxicity was not observed with the extensive clinical use of ibandronic acid. Therefore, it remains an extrapolation from data obtained in animals

as to how close the therapeutic clinical dose is separated from a critical, potentially nephrotoxic dose in human. The non-clinical testing strategy was not restricted to estimating the risk that renal effects occur, but also investigated whether subclinical minimal renal effects, if they occur, were reversible and if there was any accumulation under chronic treatment with intermittent dosing. The theoretical consideration that a 3-monthly dosing interval equals a repetition of a single dose rather than a chronic treatment regimen was supported by modelling systemic exposure based on plasma and tissue kinetic data in animals, and on toxicological data comparing single dose effects with intermittent treatment effects at the selected reference dose level used for safety assessment. The data support the conclusion that the half-life in plasma and soft tissues results in ibandronic acid being eliminated between doses, and that accumulation does not occur.

OSTEONECROSIS OF THE JAW

In animal toxicity studies there was no preclinical signal for bone toxicity, in particular for osteonecrosis when ibandronic acid was administered at therapeutic doses. The only notable abnormalities were observed in the costochondral region of dogs treated chronically with high oral doses of ibandronic acid. There were cases of necrotic areas with gap formation and hemorrhages or slight inflammation at a daily dose of 13 mg/kg/day over 6 months Allen TR *et al.* 1991. In another study, cases of focal necrosis of bone matrix, leading to gap formation and reactive callus formation and cases of focal fibrosis of the bone marrow accompanied by edema and/or focal hemorrhage were found in dogs treated at 5 or 10 mg/kg/day over 1 year Rebel W *et al.* 1995.

The pathomechanism of osteonecrosis is unknown. Comparison of dose and exposure comparison between the affected dose levels in dogs and the therapeutic dose levels in humans provide evidence that osteonecrosis may occur only at doses causing marked to severe systemic toxicity. The absence of corresponding findings at lower doses in toxicity studies and any other bone quality compromising effects in numerous pharmacodynamic animal studies Bauss F *et al.* 2002 supports this interpretation.

The only experiment the original MAH Roche conducted specifically on the potential mechanism of osteonecrosis of the jaw (ONJ) was a pilot study to test the hypothesis that significantly higher bone concentrations in the jaw may be responsible for ONJ. The results of this pilot study conclusively disproved this hypothesis, and demonstrated similar drug uptake in long bones, vertebrae and mandibles. Consequently, no further studies were conducted Bauss F *et al.* 2008. These results are consistent with the results of an earlier study with IV alendronate Lin JH *et al.* 1991 in which the uptake of ibandronic acid in the mandible was shown to be relatively similar to that in other bones of the skeleton.

ANAPHYLAXIS

Several preclinical tests and investigations were performed which raised no suspicion of ibandronic acid possessing antigenic properties. A skin sensitization test in guinea pigs was negative after intracutaneous and local application (report 408425). Furthermore, the antigenicity of ibandronic acid was investigated in guinea pigs, revealing further negative results. In particular, active systemic and passive cutaneous anaphylactic reactions were tested as well as passive hemagglutination anaphylactic reactions (report 408399). These tests confirmed the expectation of ibandronic acid having a low immunogenic potential due to its low molecular weight of 359.24 Daltons. For antibody testing via an ELISA technique, ibandronic acid was coupled with high molecular weight carriers.

OTHER TARGET ORGANS

Systemic adverse effects on other target organs, e.g. the liver or respiratory tract, were not further discussed, as they generally occurred at doses higher than the reference dose levels used for the

renal safety assessment. The risk of cancer in humans was assessed in three long-term carcinogenicity tests in two species. Ibandronic acid was administered by continuous oral administration in drinking water or by oral gavage. No evidence of carcinogenic potential was found.

The reproductive toxicology results were not reconsidered here, as the target population is postmenopausal women. The potential for genotoxicity, local tolerance, skin irritation and sensitization were tested for ibandronic acid using standard tests. From these tests, the only result of clinical relevance might be the corrosive potential to mucous membranes of the oral route of ibandronic acid.

SAFETY PHARMACOLOGY AND OTHER SAFETY STUDIES

Several studies were conducted to determine the safety pharmacology of ibandronic acid. Doses used in these studies (0.1–3.0 mg/kg for parenteral administration [IV, intraperitoneal (IP), subcutaneous (SC)] and 5–10 mg/kg for the oral study in dogs) were considerably higher than those used in clinical studies. Ibandronic acid had no effect on the central nervous system when tested in the Irwin behavioral test, nor did it show any potentiation of urethane anesthesia. Ibandronic acid had no effect on locomotor activity or on pentetrazole-induced seizures. Ibandronic acid had no analgesic effects (central nervous system) in mice, and no effects on the peripheral nervous system. Ibandronic acid did not affect intestinal motility in the mouse, gastric acid secretion in the anaesthetized rat, or heart rate or blood pressure in normotensive rats. When tested in conscious dogs, it did not alter any measured circulatory, respiratory, or Electrocardiogram parameters. IV ibandronic acid did not alter urine volume or electrolyte excretion in dogs, although higher doses did increase potassium/sodium (K+/Na+). Neither body temperature nor blood glucose concentrations were affected in conscious rabbits treated with ibandronic acid. In an assay for its potential to prolong the QT/QTc interval, ibandronic acid at a concentration of 30 µM (>10mg/mL), which is approximately 10 times the maximum concentration (Cmax) in humans, did not result in a block of repolarising currents through hERG K+ channels in vivo.

Ibandronic acid was not found to be a functional antigen, nor did it affect cytokine secretion in human peripheral blood cells in vitro. Hemolytic effects on human blood cells in vitro were detected only at concentrations about 6 000 times above the Cmax in humans (of 1 mg/mL).

DRUG INTERACTIONS

IV injections of 0.1 mg/kg/day on seven consecutive days to male and female rats indicated that ibandronic acid is unlikely to produce drug-drug interactions thro ugh a hepatic induction and/or inhibition mechanism in humans. Renal excretion of ibandronic acid in male and female rats indicated that ibandronic acid is not excreted by any known anionic or cationic transport systems.

Safety concerns from non-clinical studies are summarized in table below:

Table SII.1 Summary of safety concerns from non-clinical studies

Key Safety findings (from non-clinical studies)	Relevance to human usage
Risk of acute tubular necrosis in the kidney with repeated high IV doses given daily, weekly or two-weekly.	Risk of acute tubular necrosis in the kidney if Bonviva is administered IV at treatment intervals of less than 3 weeks or in case of an inadvertent IV overdose.
Risk of upper intestinal tract irritation due to the corrosive potential of ibandronic acid.	Risk of esophageal irritation if Bonviva tablets are taken not in accordance with the instructions described in the package insert or if broken tablets are swallowed.

IV = Intravenous

NEED FOR ADDITIONAL NON-CLINICAL DATA IF THE PRODUCT IS TO BE USED IN SPECIAL POPULATIONS

There is no need for additional non-clinical data in special populations of the target population as there are now many years of clinical study data with ibandronic acid, and about twenty years of post-marketing experience with Bondronat and ten years with Bonviva.

CONCLUSIONS ON NON-CLINICAL DATA

List of safety concerns from non-clinical data that have:

- been confirmed by clinical data
- have not been adequately refuted by clinical data
- which are of unknown significance or where further research needed

Safety Concerns	
Important identified risks (confirmed by clinical data)	Severe esophageal irritation
Important potential risks (not refuted by clinical data or which are of unknown significance)	Renal dysfunction
Missing information	None

Part II: Module SIII - Clinical trial exposure

Cumulative exposure

The estimated cumulative exposure to ibandronic acid, placebo, and other investigational medicinal products (IMPs) from Roche -interventional clinical trials where ibandronic acid was used as an investigational drug is presented in Table SIII.1. Up to the DLP 31 March 2022, an estimated total of 28,602 patients have received ibandronic acid via clinical trial participation.

Table SIII.1: Cumulative Patient Exposure to Ibandronic Acid Administered as an Investigational Drug in Clinical Trials

Stratum	Trial Status	Investigated Product, N	Other IMPs, N	Placebo, N
Oncology	Completed	3150	385	441
Osteoporosis	Completed	24,902	3384	3983
Healthy Volunteers	Completed	431	0	32
Other	Completed	119	0	0
Total		**28,602**	**3769**	**4456**

IMP= Investigational Medicinal Product, N= Total number of patients.

Cumulative exposure to ibandronic acid by demographic characteristics for Roche and Chugai-sponsored interventional clinical trials conducted with ibandronic acid as an investigational drug is presented in Table SIII.2. Due to differing reporting conventions during the time this product was under development, a breakdown of demography was not always reported.

Table SIII.2: Cumulative Exposure to Ibandronic Acid in Roche and Chugai- Sponsored Interventional Trials by Patient Demographic Characteristics

Demographic Characteristic	Indications				Total
	Oncology	Osteoporosis	Healthy Volunteers	Other	
Age					
< 18	0	0	0	0	0
≥ 18 and < 65	1,615	6,044	431	59	8,149
≥ 65	405	8,043	0	45	8493
Unknown	1130	10,815	0	15	11,960
N	**3,150**	**24,902**	**431**	**119**	**28,602**
Sex					
Female	2,556	24,432	78	48	27,114
Male	393	234	353	71	1051
Unknown	201	236	0	0	437
N	**3,150**	**24,902**	**431**	**119**	**28,602**
Race/Ethnicity					
American Indian or Alaska Native	0	7	0	0	7
Asian	30	1,833	33	2	1,898
Black or African American	12	205	4	0	221
Multiple	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Other	65	541	5	0	611
White	1,848	17,849	243	71	20,011
Unknown	1,195	4467	146	46	5854
N	**3,150**	**24,902**	**431**	**119**	**28,602**

N= Total number of patients.

The exposure data derived for the 3 mg/3 ml solution for injection, the 150 mg tablets and the 2.5 mg tablets was derived from the pooled clinical study database and is presented for populations in the double-blinded, randomized, controlled clinical studies (the randomized blinded population) in Table SIII.3 and for all exposed patients (the long term exposure population) in Table SIII.4.

Table SIII.3: Exposure by Duration-Randomized Blinded Population (Post Menopausal Osteoporosis)

Treatment Group			
Ibandronic acid	**2.5 mg tablets**	**150 mg tablets**	**3 mg solution for injection**
Durations of Exposure (months)	N=860 n (person years)	N=1279 n (person years)	N=469 n (person years)
Cumulative up to 1 m	859 (70.7)	1279 (106.6)	469 (39.1)

Cumulative up to 3 m	839 (207.3)	1279 (313.3)	469 (117.2)
Cumulative up to 6 m	810 (400.9)	1229 (607.2)	426 (212.9)
Cumulative up to 12 m	779 (768.9)	1180 (1162.5)	413 (409.2)
Cumulative up to 18 m	745 (1112.2)	1121 (1341.3)	399 (593.7)
Cumulative up to 24 m	723 (1433.9)	333 (658.7)	380 (756.3)
Cumulative up to 28 m	259 (521.7)	147 (295.4)	163 (328.3)
Cumulative up to 32 m	0	0	0
Total	**859 (1506.2)**	**1279 (1566.7)**	**469 (809.6)**

m = month; N = number.

Note: Studies BM16549 and BM16550 were 2 years in length, study MM17385 was 1 year in length.

Table SIII.4: Exposure by Duration-Long-term Exposure Population (Post Menopausal Osteoporosis)

Treatment Group		
Ibandronic acid	**150 mg tablets monthly**	**3 mg solution for injection quarterly**
Durations of Exposure (months)	N=1,464 n (person years)	N=606 n (person years)
Cumulative up to 1 m	1,464 (122.0)	606 (50.5)
Cumulative up to 3 m	1,464 (359.4)	606 (151.5)
Cumulative up to 6 m	1,413 (699.0)	561 (280.4)
Cumulative up to 12 m	1,360 (1341.8)	548 (544.2)
Cumulative up to 18 m	1,299 (1607.7)	534 (795.9)
Cumulative up to 24 m	508 (1009.6)	514 (1026.4)
Cumulative up to 36 m	431 (1200.4)	447 (1282.9)
Cumulative up to 48 months	266 (965.9)	302 (1159.5)
Cumulative up to 60 months	166 (825.5)	247 (1228.8)
Cumulative up to 64 months	118 (605.0)	214 (1104.6)
Cumulative up to 68 months	0	4 (21.4)
Cumulative up to 72 months	0	0
Total	1,464 (2606.0)	606 (1997.1)

m = month; N = number.

Note: Studies BM16549 and BM16550 were 2 years in length, study MM17385 was 1 year in length, studies MA17903 and MA17904 were 3 years in length.

Patients have a maximum of 5 years exposure.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

New safety signals have been detected and/or have been further specified during the post-marketing period in PMO. These new safety concerns are addressed in Part II: Module SVII - Identified and potential risks.

Based on the specifics of the designs of five studies and in order to assure quality data for marketed doses, the following two populations were analyzed for exposure by different categories and for the corresponding risks.

Randomized Blinded Population

This population includes patients from clinical studies in which the treatment was randomized and the patients were blinded to the treatment allocated. This population includes patients from the 3 mg/3 ml IV solution for injection, 150 mg oral and 2.5 mg oral treatment groups of studies BM16549, BM16550 and MM17385.

Long-term exposure population

This population includes patients from all five clinical studies, including open-label extension studies, in which the treatments of interest, i.e., oral 150 mg monthly and 3 mg/3 ml IV every three months, were administered. This population includes patients who had the 3 mg/3 ml IV solution for injection or 150 mg oral treatment periods in studies BM16549, MA17903, BM16550, MA17904 and MM17385 at any time.

The subgroups of postmenopausal women excluded from clinical studies of IV and oral ibandronic acid in PMO included those with significant medical conditions, malignant diseases, allergy to bisphosphonates, contraindications for calcium or vitamin D therapy, serum calcium >10.5 mg/dL or <8.0 mg/dL, vitamin D deficiency, WBC <2500/µL, ALT greater than twice the upper limit of normal range, serum albumin <3.0 g/dL, renal impairment (serum creatinine > 2.4 mg/dL) or history of major GI disease.
Contraindications in the EU SmPC include hypocalcemia and hypersensitivity to ibandronic acid. Despite these, it cannot be ruled out that in clinical practice some patients from these subgroups may receive treatment with ibandronic acid. The exclusion criterion of major GI disease was the presence of medically significant GI disease, such as esophageal abnormalities and gastric ulcers.

PMO:

Information on the major exclusion criteria of the pivotal studies for the 3 mg/3 ml solution for injection (BM16650), and the 150 mg tablet (BM16549, MM17385) is given in Table SIV.1.1. The major exclusion criteria were identical for both of these trials.

Table SIV.1.1 Overview of Exclusion Criteria in Clinical studies (Post Menopausal Osteoporosis)

Study Number	No. of PMO Patients	Age Range	Main Exclusion Criteria for Study
BM16549 (MOBILE)	1602	54-81	• Serum calcium >10.5 mg/dl or <8.0 mg/dl • Renal impairment (serum creatinine > 2.4 mg/dl) • WBC <2500/µl significant medical conditions • Serum albumin <3.0 g/dl • ALT > twice upper limit of normal range • Malignant diseases • Allergy to bisphosphonates • Contraindications for calcium or vitamin D therapy • Vitamin D deficiency (serum 25-hydroxy vitamin D < 10ng/ml) • History of major gastrointestinal disease

BM16550 (DIVA)	1395	54-80	• Serum calcium >10.5 mg/dl or <8.0 mg/dl • Renal impairment (serum creatinine > 2.4 mg/dl) • WBC <2500/µl significant medical conditions • Serum albumin <3.0 g/dl • ALT > twice upper limit of normal range • Malignant diseases • Allergy to bisphosphonates • Contraindications for calcium or vitamin D therapy • Vitamin D deficiency (serum 25-hydroxy vitamin D <10ng/ml) • History of major gastrointestinal disease
MM17385 (MOTION)	1733	55-84	• Serum calcium >10.5 mg/dl or <8.0 mg/dl • Renal impairment (serum creatinine > 2.4 mg/dl) • WBC <2500/µl significant medical conditions • Serum albumin <3.0 g/dl • ALT > twice upper limit of normal range • Malignant diseases • Allergy to bisphosphonates • Contraindications for calcium or vitamin D therapy • Vitamin D deficiency (serum 25-hydroxy vitamin D <10ng/ml) • History of major gastrointestinal disease

Oncology:

The information for exclusion criteria for oncology studies is presented in Table SIV.1.2. The major exclusion criteria were same in all the studies.

Table SIV.1.2 Overview of Exclusion Criteria in Clinical studies (Oncology)

Study Number	No. of Patients	Main Exclusion Criteria for Study
MF 4265	305	Previous bisphosphonate or gallium treatment within last six months Administration of any investigational drug within 30 days preceding the first dose of the study drug • Life expectancy < 60 weeks • Pregnancy or lactation period • Hypercalacemia • Hypocalcaemia • Paget's disease of the bone • Primary hyperparathyroidism • Known liver/brain metastases • High dose chemotherapy • Aspirin-sensitive asthma in medical history Pretreatment within 4 weeks prior to the start and treatment with aminoglycoside antibiotics during study • Serum albumin > 3.0 mg/dl • Allergy to bisphosphonates • History of major gastrointestinal disease

MM4414	285	• Previous bisphosphonate or gallium treatment within last six months • Administration of any investigational drug within 30 days preceding the first dose of the study drug • Life expectancy < 60 weeks • Pregnancy or lactation period • Hypercalacemia • Hypocalcaemia • Paget's disease of the bone • Primary hyperparathyroidism • Known liver/brain metastases • High dose chemotherapy • Aspirin-sensitive asthma in medical history • Serum albumin > 3.0 mg/dl • Allergy to bisphosphonates • -History of major gastrointestinal disease
MF4434	285	Previous bisphosphonate or gallium treatment within last six months Administration of any investigational drug within 30 days preceding the first dose of the study drug • Life expectancy < 60 weeks • Pregnancy or lactation period • Hypercalacemia • Hypocalcaemia • Paget's disease of the bone

Study Number	**No. of Patients**	**Main Exclusion Criteria for Study**
		• Primary hyperparathyroidism • Known liver/brain metastases • High dose chemotherapy • Aspirin-sensitive asthma in medical history • Serum albumin > 3.0 mg/dl • Treatment with aminoglycoside antibiotics • Allergy to bisphosphonates • History of major gastrointestinal disease

Exclusion criteria which will remain as contraindications	
Criteria	**Implications for target population**
Hypocalcemia	Bonviva, like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values. Existing hypocalcemia 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.
Hypersensitivity	Ibandronic acid is contraindicated in patients with known hypersensitivity to ibandronic acid or to any of the excipients, due to an increased risk of anaphylaxis.

Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia	Adverse experiences such as esophagitis, esophageal ulcers and esophageal erosions, in some cases severe and requiring hospitalization, rarely with bleeding or followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. Bonviva and Bondronat film-coated tablets are contraindicated in patients with abnormalities of the esophagus as orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa that may lead to worsening of underlying disease.
Inability to stand or sit upright for at least 60 minutes	Bonviva and Bondronat film-coated tablets are contraindicated in patients with inability to stand or sit upright for at least 60 minutes.

Source: Bonviva and Bondronat SmPCs

Exclusion criteria which are NOT proposed to remain as contraindications

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Ability to detect adverse reactions	**Limitation of trial programme**	**Discussion of implications for target population**
Which are rare (it may be appropriate to choose other ADR frequencies)	28,602 patients have received Bonviva/Bondronat treatment in Roche sponsored investigation clinical trials since the start of the clinical development programme. Very rare events may not be detected within the clinical development programme	Reports of rare adverse reactions are detected and managed in the post-marketing setting according to routine pharmacovigilance procedures.
Due to prolonged exposure	Exposure in clinical development up to 1-3 years (pivotal trials) and 5 years (long-term extension trials). There is a rather limited number of patients in the pooled clinical study database treated either with the 150 mg tablet monthly (1,279 patients) or the 3 mg IV solution (469 patients) every three months. Therefore, AEs due to prolonged exposure	In combination with the established safety profile in the pivotal clinical trials (MF4411, MF4380, BM16549, BM16550, with an exposure of more than 15 000 patient-years), ongoing pharmacovigilance activities to further detect and characterize risks, and the MAH process that serious adverse events

	may not be reliably detected.	(SAEs) of all clinical studies as well as serious and non-serious spontaneous events from the post- marketing setting are reported and monitored in the pharmacovigilance database, the current clinical database for both presentations is considered adequate.
Due to cumulative effects	Exposure in clinical development up to 1-3 years (pivotal trials) and 5 years (long-term extension trials). There is a rather limited number of patients in the pooled clinical study database treated either with the 150 mg tablet monthly (1,279 patients) or the 3 mg IV solution (469 patients) every three months. Therefore, AEs due to cumulative effects may not be reliably detected.	Reports of cumulative effects are detected and managed in the post-marketing setting according to routine pharmacovigilance procedures.
Which have a long latency	ONJ and atypical femoral fracture are suggested to be associated with long-term BP use	Long latency adverse drug reactions are defined as adverse drug reactions (ADRs) which occur six months or more after initial exposure. Bonviva is dosed monthly/ quarterly. Bondronat every other day/ every 3-4 weeks months. Based on the review of the safety profile for Bonviva/ Bondronat, there is no evidence for Bonviva/ Bondronat induced long latency adverse drug reactions.

ADR= adverse drug reactions; BP=bisphosphonate; ONJ=osteonecrosis of jaw; EU SmPC=European Union Summary of product characteristics.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program.

Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment	Patients with ALT >twice upper limit of normal range were excluded from the key clinical studies in postmenopausal osteoporosis. Therefore, not included in the clinical development program.
• Patients with renal impairment	97 patients with renal impairment were included in the following clinical trials: MF7148, MF7169 and WP18551.
• Patients with malignant disease	Not included in the clinical development program.
• Patients with history of major gastrointestinal disease	Not included in the clinical development program.
Population with relevant different ethnic origin	Cumulative exposure in clinical development programme by ethnicity: American Indian or Alaska Native: 7 Asian: 1,898 Black or African American: 221 Multiple: 0 Native Hawaiian or Other Pacific Islander: 0 Other: 611 White: 20,011 Unknown: 5854
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Method used to calculate exposure

Estimates of patients exposed to commercial ibandronic acid are based on the numbers of packs sold.

Until June 2017, the package unit volume data for product Bondronat/ Bonviva was sourced from Roche supply chain and financial systems (Controlling Profitability Analysis). From July 2017 until the DLP of the current report in June 2021, sales data was sourced from the Atnahs Pharma supply chain. The sales records are provided on a monthly basis; therefore, cumulative and interval exposure is presented to the nearest point of DLP for the most recent Periodic Safety Update Report (PSUR) i.e., 30 June 2021.

Roche and Atnahs Pharma do not have access to demographic information (age and sex) for patients who have taken ibandronic acid across various geographies.

Bonviva

The patient exposure calculation is based on the new prescription/ total prescription ratio which is assumed to be 30% new patients in a year.

Bondronat

Vials:

- Each vial of 6 mg/6 ml, 1 mg/1 ml sold represents 1 patient.
- It is assumed that 70% of patients receive 2 mg single infusion and 30% receive 2, 2 mg single infusion (a limited number of patients may receive a second infusion in cases of recurrence or insufficient efficacy) for the treatment of hypercalcaemia.

Film-coated tablets 50 mg:

- Each 4-week course of 28 tablets pack sold in a particular month represents a single patient exposure, assuming 12-month average treatment duration in MBD.

Until 30 June 2021, an estimated cumulative total of 45.7 million patients have received ibandronic acid (Table SV.1.1) from marketing experience.

Cumulatively, a total of approximately 43.7 million patients have received Bonviva and 1.9 million have received Bondronat through marketing experience.

Table SV.1.1 Cumulative Exposure from Marketing Experience

Period	Region	Product	Number of patients
IBD - Jun 2012	Global	Bonviva	28,164,774
		Bondronat	1,439,582
Jul 2012 - Jun 2017	United States	Boniva	153,537
Jul 2012 - May 2018	EEA	Bonviva	4,055,919
	RoW		4,232,690

	Japan		1,195,061
	EEA	Bondonat	97,718
	ROW		151,310
Jun 2018 – Jun 2021	EEA	Bonviva	762,512
	RoW		1,778,575
	Japan		3,384,088
	EEA	Bondonat	25,676
	ROW		264,200
Total		**Bonviva**	**43,727,156**
		Bondronat	**1,978,486**
		Total	**45,705,642**

EEA: European Economic Area, IBD: International Birth Date, RoW: Rest of the World
Note: Rounding errors may be introduced in the total figure.

Other Post-Authorisation Use

To the best knowledge of the MAH, the current general pattern of use for the vast majority of patients taking Bonviva/ Bondronat is consistent with the product's labelling and current guidelines for both osteoporosis and MBD.

Based on continuous review of the literature, the MAH is aware that Bonviva and Bondronat have been used in indications other than those currently in the label (e.g. for Bonviva: male osteoporosis, glucocorticoid induced osteoporosis [which are indications of other bisphosphonates], juvenile rheumatoid arthritis as well as prevention of bone loss in haemodialysis, liver transplant patients, etc.; for Bondronat: cancer patients without established bone metastases, cancer treatment induced bone loss and for the treatment of bone pain etc.) Hakala *et al.* 2012, Azim *et al.* 2013, Lester *et al.* 2012, Valiyeva *et al.* 2013, Kaemmerer D *et al.* 2012, Ottanelli S. 2015. Maier *et al.* 2016, Shin *et al.* 2017, Wang *et al.*, 2016.

No specific relevant safety data were available with respect to off-label or other patterns of use of ibandronic acid.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

It is not believed that there is potential for ibandronic acid to be used for illegal purposes. There are no cases of abuse, dependency or withdrawal effects reported, and none would be expected based on the pharmacological properties. No further measures are proposed.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The safety concern termed "atypical femoral fracture", previously classified as important potential risk was revised to "atypical fractures of long bones" and reclassified as an important identified risk.

Evidence for the reclassification and expansion of the risk term was identified during the evaluation of a validated signal for atypical fractures at sites other than the femur with ibandronic acid, conducted on 27 September 2021 Atnahs Pharma UK Ltd. 2021. The signal assessment report was triggered following a request from the Pharmaceuticals and Medical Devices Agency (PMDA), Japan to update the local product information to include atypical fractures at other sites than the femur.

A review of literature sources during the signal evaluation revealed evidence from epidemiological studies suggesting an increased risk of atypical fractures of long bones with the long-term use of ibandronic acid, and a comparable mechanism of action compared with other bisphosphonates, a finding which was supported by significant ICSR data.

Based on the long term and well-established efficacy and safety profile of ibandronic acid, the overall benefit -risk balance for the product remains positive, and the proposed actions of reclassifying atypical fractures of long bones to an important identified risk and the updating of SmPC and PIL are deemed sufficient by the MAH.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

<table>
<tr><th colspan="2">Important identified risk: Osteonecrosis of the Jaw</th></tr>
<tr><td>Potential mechanism(s):</td><td>Ibandronic acid belongs to the group of nitrogen-containing BPs, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. The exact pathogenesis of ONJ is unknown and no evidence–based therapeutic protocols exist for treating this condition. Diagnostic criteria are not well-established, inclusion and exclusion criteria in reported cases are lacking and no animal models have been established to adequately study this condition.</td></tr>
<tr><td>Evidence source(s) and strength of evidence:</td><td>Post-marketing experience.</td></tr>
<tr><td>Characterisation of the risk:</td><td>Epidemiologic data suggest an incidence in clinical use ranging from 1/250,000 (from Germany) to 1/160,000 worldwide Watts N B. et al. 2008.
Frequency with 95%CI:
Randomized, blinded trial population
2.5 mg daily | 150 mg monthly | 3 mg IV n / N (%) n/ N (%)
0 / 860 | 0 / 1,279 | 0 / 469
ONJ was not observed in the randomized blinded trial population nor in the long-term exposure population.

Background incidence/prevalence in Females with PMO
Incidence (estimated from literature): ca. 0.7 per 100,000 person years Capsoni F. 2008
Prevalence (estimated from literature): < 1 per 100,000 in Europe up to 4 cases in 10,000 in Australia</td></tr>
</table>

	Background incidence/prevalence in cancer Incidence in clinical trials (patients treated with denosumab or zoledronic acid) — 1.3% - 2% Stopeck A *et al.* 2009,Fizazi *et al.* 2010, Henry D *et al.* 2009. Incidence in observational studies — 1.1% - 18.6% Walter C *et al.* 2009, Christodoulou-C *et al.* 2009 (patients treated with bisphosphonates) **PMO** The worldwide incidence of ONJ is rare in the PMO population, Grbic JT *et al.* 2008, Watts N B. *et al.* 2008. Reviews of European literature revealed the incidence to be 0.7 per 100 000 person-years cases Capsoni F. 2008, Carey JJ *et al.* 2008, Capsoni F *et al.* 2006 and a prevalence rate ranging from 0.0259% to 0.00038% for ONJ in the oral bisphosphonate treated PMO population Grbic JT *et al.* 2008 , Khan AA *et al.* 2009. Khan A. 2008. There are no published reports of ONJ related mortality in the PMO population. **Oncology** Data on the incidence of ONJ in oncology patients with bone metastases is available from denosumab phase III clinical trials. Incidence ranged from 1.3% - 2% in patients breast cancer, prostate cancer, multiple myeloma, and other cancers treated with denosumab or zoledronic acid Stopeck A *et al.* 2009, Fizazi K *et al.* 2010, Henry D *et al.* 2009. The incidence of ONJ among patients treated with bisphosphonates has varied widely among observational studies ranging from 1.1% -18.6% Walter C *et al.* 2009, Christodoulou C *et al.* 2009, McArthur HL *et al.* 2008. Among these, the two largest observational studies suggest a low incidence of ONJ. In a large medical chart review of 4019 cancer patients treated with IV pamidronate and/or zoledronic acid, the incidence of ONJ was 1.2% among 1338 breast cancer patients and 2.4% among 548 multiple myeloma patients (Hoff AO *et al.* 2008 also cited in Walter *et al.* 2009. No cases were observed in patients with other tumor types, which included renal cell, lung and prostate cancers. In a large medical chart review study at the Memorial Sloan-Kettering Cancer Center, the incidence of ONJ was 1.1% among 6561 cancer patients (breast cancer, multiple myeloma, prostate cancer, lung cancer and other) treated with IV pamidronate and/or zoledronic acid McArthur HL *et al.* 2008 . In summary, among IV bisphosphonate regimens, the incidence ONJ is infrequent as reported in phase III trials (<= 1% up to 1.4%). Observational studies report incidence proportions of 1.1-18.6% for bisphosphonate-containing regimens. The lack of standard definitions for ONJ, small sample sizes, and differences in risk factors (such as treatments, dental procedures) among patients may have led to variation between studies.
Risk factors and risk groups:	Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g. chemotherapy (including angiogenesis inhibitors Ruggiero SL *et al.* 2014 radiotherapy, corticosteroids), and co-morbid disorders (e.g. anemia, coagulopathy, infection, pre-existing dental disease, tobacco use and advanced age).

	Risk factors can be however categorized as follows Kanis JA *et al.* 2008. – Local (periodontal diseases, denture trauma (e.g. dental extraction), local malignancy, other concomitant oral diseases) – Demographic (age, race, cancer diagnosis, corticosteroid therapy, diabetes, smoking, alcohol use, poor oral hygiene, and chemotherapeutic drugs Tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily IV administered BPs. Many of these patients were also receiving chemotherapy and corticosteroids. ONJ has also been reported in patients with osteoporosis receiving oral BPs (in the osteoporosis setting). High doses clearly exceeding the IV and oral Bonviva dose for PMO are a risk factor of ONJ Goh SK *et al.* 2007, Odvina CV *et al.* 2005, Lee P *et al.* 2008. ONJ is more common in the oncology indication as compared to PMO indication. **Oncology** Data on the incidence of ONJ in oncology patients with bone metastases is available from denosumab phase III clinical trials. Incidence ranged from 1.3% - 2% in patients breast cancer, prostate cancer, multiple myeloma, and other cancers treated with denosumab or zoledronic acid Stopeck A *et al.* 2009, Fizazi K *et al.* 2010, Henry D *et al.* 2009. The incidence of ONJ among patients treated with bisphosphonates has varied widely among observational studies ranging from 1.1% -18.6% Walter C *et al.* 2009, Christodoulou C *et al.* 2009, McArthur HL *et al.* 2008. Among these, the two largest observational studies suggest a low incidence of ONJ. In a large medical chart review of 4019 cancer patients treated with IV pamidronate and/or zoledronic acid, the incidence of ONJ was 1.2% among 1338 breast cancer patients and 2.4% among 548 multiple myeloma patients (Hoff AO *et al.* 2008 also cited in Walter *et al.* 2009. No cases were observed in patients with other tumor types, which included renal cell, lung and prostate cancers. In a large medical chart review study at the Memorial Sloan-Kettering Cancer Center, the incidence of ONJ was 1.1% among 6561 cancer patients (breast cancer, multiple myeloma, prostate cancer, lung cancer and other) treated with IV pamidronate and/or zoledronic acid McArthur HL *et al.* 2008 . In summary, among IV bisphosphonate regimens, the incidence ONJ is infrequent as reported in phase III trials (<= 1% up to 1.4%). Observational studies report incidence proportions of 1.1-18.6% for bisphosphonate-containing regimens. The lack of standard definitions for ONJ, small sample sizes, and differences in risk factors (such as treatments, dental procedures) among patients may have led to variation between studies.
Preventability:	A dental examination with appropriate preventive dentistry should be considered prior to treatment with BPs in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on BP therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of BP treatment reduces the risk of ONJ. Clinical judgment of the

	treating physician should guide the management plan of each patient based on individual benefit/risk assessment.
Impact on the risk-benefit balance of the product:	In the most severe cases, patients can experience extensive tooth loss and bone damage, with insufficient healthy bone for successful implants or dentures Shane E *et al.* 2010.
Public health impact:	None

Important identified risk: Severe oesophageal irritation (only for oral ibandronate)	
Potential mechanism(s):	The mechanism by which BPs injure the upper mucosa is not fully understood, however the animal studies, clinical trial data and experience in patients show that BPs cause esophageal irritation in areas of direct contact, especially when acid is present, strongly suggesting topical etiology of injury. Clinical trials comparing BPs to NSAID, known GI irritators, have shown that in contrast to NSAIDs, BPs do not show systemic inhibition of cyclooxygenase resulting in decreased synthesis of protective PGE2. The evidence from animal data suggests that BP mucosal injury is topically induced. Studies with alendronate and pamidronate have shown concentration-dependent decrease in transmural potential difference, weakening of phospholipid barrier of the gastric mucosa which followed by extensive injury with neutrophil infiltration in the epithelium and significant increase in the level of PGE-2 strongly suggest topical mucosal injury. Furthermore, IV administration of alendronate or pamidronate in animal models has not induced mucosal injury. Based on the above, there is strong evidence that BP induced injury is caused by the contact with mucosa, and any measures reducing the probability of contact can prevent the injury. This also has been confirmed by the fact, that after the enhancement of administration instructions for BPs (to be taken with a full glass of water when staying upright for the period of time) the frequency of the reports of upper GI irritation have dramatically reduced for oral BPs Schoonderwoerd BA *et al.* 2008.
Evidence source(s) and strength of evidence:	A UK GRPD analysis revealed that subjects with osteoporosis not taking bisphosphonates had a higher incidence of upper GI tract events compared with sex-age matched non-osteoporosis group (incidence rates of 2.8% versus 1.8%) Cryer B *et al.* 2002, Van Staa T *et al.* 1997. Similarly, a United States Health Maintenance Organization (US HMO) study concluded that osteoporosis was a potential confounder for the alendronate-GI perforation, bleeding, and ulcer relationships Donahue JG *et al.* 2002. A member of the FDA's division of drug risk assessment submitted a letter to the editor of the New England Journal of Medicine Wysowski DK. 2009. Further, there was an FDA posting on potential signals associated with oral bisphosphonates as it pertains to esophageal cancer (Feb 4, 2009). http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm085925.htm. 2008. One small study of 154 breast cancer patients treated with either radiotherapy plus chemotherapy or radiotherapy alone found that 28% of patients treated with radiotherapy plus chemotherapy and 5% of patients treated with radiotherapy alone developed moderate or severe esophagitis/dysphagia Fiets WE *et al.* 2003.

Characterisation of the risk:	Frequency with 95%CI Randomised, blinded trial population *2.5 mg daily n/N (%)* — *150 mg monthly n/N (%)* — *3 mg IV* n/N (%) 22/860 (2.56%) — 15/1279 (1.1%) — 9/469 (1.92%) Long term exposure population *150 mg monthly n/N (%)* — *3 mg IV n/N (%)* 23 1,464 (1.57%) — 20/606 (3.30%) Unadjusted Relative Risk and Risk Difference with 95% CI Randomised blinded population Relative risk (95% CI) — Risk difference (95% CI) 150 mg monthly: 0.46 (0.24, 0.88) — -0.01 (-0.03, -0.00) 3mg IV: 0.75 (0.35, 1.62) — -0.01 (-0.02, -0.01) Background Incidence/ Prevalence of Oesophageal Irritation (UK GPRD Epi data) *Age Range (years)* — *Incidence in Females per 1000 Person Years* — *Prevalence in Females (%)* *50-59*: 16.9 — 12% *60-69*: 18.6 — 15% *70-79*: 19.2 — 18% *>80*: 14.5 — 16% Background Incidence in Breast Cancer 5% of breast cancer patients treated with radiotherapy alone; 28% of breast cancer patients treated with radiotherapy plus chemotherapy Rizzoli-R *et al.* 2010.
Risk factors and risk groups:	Risk factors of esophageal irritation are: Slow-release medications Lip GY *et al.* 1995, Bourke T *et al.* 2009, Novo G *et al.* 2008 and duodenal juice/acid reflux Lip GY *et al.* 2008, Iguchy Y *et al.* 2008.
Preventability:	Avoidance of risk factors and adherence to special dosing instructions to oral BPs.
Impact on the risk-benefit balance of the product:	Regarding severe oesophageal irrigation, the impact on the patient quality of life is considered low
Public health impact:	Minimal

Important identified risk: Acute Phase Reaction	
Potential mechanism(s):	Acute-phase response is a nonspecific physiologic reaction associated with increased levels of inflammatory cytokines like IL- 6 and tumor necrosis factor-alpha Dicuonzo G *et al.* 2003, Thiebaud D *et al.* 1997, and accompanied by fever, and flu like symptoms including fatigue, nausea, arthralgia and myalgia. The APR is maximal within 28 to 36 hours of IV

<table>
<tr><td></td><td>administration and disappears 2 to 3 days later, despite continuing treatment Dicuonzo G et al. 2003, Donahue JG et al. 2002, Santini D et al. 2007, Thiebaud D et al. 1997. Treatment with histamine blockers, antipyretic or corticosteroids may reduce symptoms Cole Z et al. 2008.</td></tr>
<tr><td>Evidence source(s) and strength of evidence:</td><td>Intravenous nitrogen-containing bisphosphonates are known to cause an adverse event resembling the APR Adami S et al. 1987.</td></tr>
<tr><td>Characterisation of the risk:</td><td>Frequency with 95%CI

Randomized, blinded trial population
<table><tr><th>2.5 mg daily
n / N (%)</th><th>150 mg monthly
n / N (%)</th><th>3 mg IV
n / N (%)</th></tr><tr><td>10 / 860 (1.16%)</td><td>45 / 1,279 (3.52%)</td><td>23 / 469 (4.90%)</td></tr></table>
Long term exposure population
<table><tr><th>150 mg monthly
n / N (%)</th><th>3 mg IV
n / N (%)</th></tr><tr><td>45 / 1,464 (3.07%)</td><td>25 / 606 (4.13%)</td></tr></table>
Unadjusted Relative Risk and Risk Difference with 95% CI

Randomized, blinded trial population
<table><tr><th></th><th>Relative Risk (95% CI)</th><th>Risk difference (95% CI)</th></tr><tr><td>150 mg monthly</td><td>3.03 (1.53, 5.79)</td><td>0.02 (0.01, 0.04)</td></tr><tr><td>3 mg IV</td><td>4.22 (2.02, 8.79)</td><td>0.04 (0.02, 0.06)</td></tr></table>
Background incidence of bisphosphonates treatment

PMO

The incidence of flu syndrome was 4.1% (39 of 949), and the crude rate of influenza-like illness was 0.2% (2 of 975) for the placebo treatment groups in the two pivotal clinical studies of 36 months duration, MF4380 (IV) and MF4411 (oral).

Oncology

The incidence of flu syndrome was 5.3% (8 of 152), and the crude rate of flu syndrome was 1.3% (2 of 157) for the placebo treatment group in the pivotal IV phase III study in patients with MBD due to breast cancer (MF4265). No further unexposed prevalence and incidence data available.</td></tr>
<tr><td>Risk factors and risk groups:</td><td>No special risk groups or factors were investigated or identified.</td></tr>
<tr><td>Preventability:</td><td>The BP-induced acute-phase response is usually benign and self- limited. Awareness of the risk for the patients is further provided in the package leaflet. There are no known preventive measures.</td></tr>
<tr><td>Impact on the risk-benefit balance of the product:</td><td>The impact on the patient quality of life is considered low.</td></tr>
<tr><td>Public health impact:</td><td>None.</td></tr>
</table>

Important identified risk: Atypical fractures of long bones	
Potential mechanism(s):	The mechanism(s) for the development of atypical fractures of long bones in patients taking BPs is not known. The main postulated mechanism is (sustained over-) suppression of bone turnover leading indirectly to ageing bone and the delay or prevention of repair of naturally occurring stress fractures although the evidence is not conclusive. However other possible pathogenetic mechanisms associated with atypical fractures of long bones have been described.
Evidence source(s) and strength of evidence:	**Atypical femur fractures (AFF)** **PMO** Based on available literature, the occurrence of atypical femoral fractures for post-menopausal osteoporosis and/or over- suppression of bone turnover have been suggested to be associated with the prolonged use of bisphosphonates Visekruna M *et al.* 2008, Neviaser AS *et al.* 2008, Goh SK *et al.* 2007, Odvina CV *et al.* 2005, Lee P et al, 2008, Shane E *et al.* 2014. In EMA Responses dated 21 October 2010 EMA/CHMP/661040/2010, CHMP review under article 20 of regulation, the MAH concluded that a number of reports of subtrochanteric and diaphyseal femoral fractures with minimal or no trauma, and of non-femoral stress fractures, have been received for patients treated with ibandronate. **Oncology** After a thorough review of all available pre-clinical, clinical and published literature data, the MAH found no cases of atypical stress fracture associated with Bondronat (ibandronic acid) use in metastatic bone disease or tumor-related hypercalcaemia patients. For this reason, the MAH cannot provide any comments about any underlying pathophysiological mechanism(s) of atypical stress fractures in the case of Bondronat use in the label approved indications or provide any information regarding risk of atypical stress fractures or possible risk factors in this setting. **Atypical fractures at other sites** On 06 January 2021, The Pharmaceuticals and Medical Devices Agency (PMDA), Japan noted evidence supporting an association with ibandronic acid treatment with atypical fracture at sites other than the femur, and requested a product labelling update for Bonviva. As part of signal validation, a literature review suggested that atypical fractures of long bones, such as the ulna and tibia have also been reported in patients receiving long-term treatment Deguchi S *et al.* 2021; Handa K *et al.* 2020; Tan SH *et al.* 2015; Heo YMP *et al.* 2021; Asano Y *et al.* 2020; Moon J *et al.* 2013; Yam MG *et al.* 2017. These fractures occur after minimal, or no trauma and some patients experience prodromal pain prior to presenting with a completed fracture. The global safety database identified case reports of atypical fractures at other sites but was confounded by limited information.
Characterisation of the risk:	**Atypical femur fractures** Atypical fractures of long bones such as subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These fractures (most commonly) occur after minimal or no trauma. Confirmed reports of atypical fractures of long bones (as per ASBMR

	definition) were not observed in the ibandronic acid clinical study database. Newer evidence suggests that atypical femoral fractures are stress or insufficiency fractures Shane E *et al.* 2014. Frequency with 95% CI This risk was neither detected in the randomized, blinded trial population nor in the long-term exposure population treated with either 150 mg oral once monthly or 3 mg IV every three months. Background incidence/prevalence Atypical femoral fractures are characterized by unique radiographic (transverse fracture line, periosteal callus formation at the fracture site, little or no comminution) and clinical features (prodromal pain, bilaterality) that resemble stress fractures or reactions. The unusual radiographic features distinguish atypical femoral fractures from ordinary osteoporotic femoral diaphyseal fractures Shane E *et al.* 2014. **PMO** The overall incidence of hip / femur fractures was low in the eight clinical studies reviewed. A total of 81 / 10,647 (0.8 %) patients reported at least one fracture in the 8 clinical studies: 20 / 2,007 (1 %) patients exposed to placebo, 60 / 7,781 (0.8 %) patients exposed to ibandronic acid and 1 / 859 (0.1%) patients exposed to alendronate. Post-marketing / epidemiology data: Incidence varied with duration of BP treatment from 2:100,000 per year for 2 years duration to 78:100,000 per year for 8 years treatment duration Dell R *et al.* 2009. The cases of atypical stress fracture that have been reported so in PMO occurred after a median exposure to BPs of 5-6 years (with a minimum treatment duration of 2.5-3 years) Nieves JW *et al.* 2010. The overall incidence of subtrochanteric and shaft fractures combined is below 30 per 100,000 person-years Nieves JW *et al.* 2010. The highest estimate of the rate of atypical subtrochanteric/diaphyseal fractures of 100 per 100,000 in long-term users of alendronate has been reported in a Danish study Abrahamsen B *et al.* 2009. **Oncology** After a thorough review of all available pre-clinical, clinical and published literature data, the MAH found no cases of atypical stress fracture associated with Bondronat (ibandronic acid) use in MBD or tumor related hypercalcaemia patients. Moreover, a review of the overall medical context of MBD or malignant hypercalcaemia is supportive of the above conclusions, understanding the particularities linked to the bone structure and characteristics of the metastatic bone lesions, on one hand, and the overall treatment duration, on the other hand. Both aspects differ profoundly from what is being seen in PMO. In summary, while some epidemiology studies suggest that subtrochanteric and femoral shaft fractures may be normal osteoporotic fractures other studies suggest that long-term BP use may increase the risk of subtrochanteric and femoral shaft fractures. **Atypical fractures at other sites** A search of Atnahs safety database yielded 432 PTs of interest with 409 (94.7%) identified as long bone fracture (other than the femur). Reported atypical fractures of long bones excluding the femur accounted for 4.2% of the total number of fractures of these bones.

	There was a lack of information precluding a meaningful causality assessment in many of these case reports. Within the literature, most atypical fractures of long bones other than the femur were reported for the ulna Deguchi S *et al.* 2021; Handa K *et al.* 2020; Tan SH *et al.* 2015; Heo YMP *et al.* 2021; Asano Y *et al.* 2020; Moon J *et al.* 2013; Yam MG *et al.* 2017. The atypical fractures in these reports had similar characteristics as AFFs: noncomminuted transverse or short oblique fracture of the proximal bone, (focal) cortical thickening of the lateral cortex, sclerosis, sometimes delayed healing. The absolute number of publications is low, and the rate is a fraction of that AFF, which is considered rare. Heo YMP *et al.* 2021 concluded that AUFs occurred in patients who took bisphosphonates longer than AFFs or those whose bisphosphonates were discontinued as few years earlier. The low number of reports of atypical fractures at sites other than the femur is probably due to the difference in stress-loading of other long bones and the lack of clear definition.
Risk factors and risk groups:	Atypical fractures of long bones appear to be more common in patients who have been exposed to long - term BPs, usually for more than 3 years (median treatment 7 years) Shane E *et al.* 2014. **PMO** Risk factors identified for fractures in patients with osteoporosis are female gender in combination with advanced age due to post- menopausal estrogen deficiency Metcalfe D. 2008. Patients with concomitant diseases requiring long-term glucocorticoid administration (e.g., rheumatoid arthritis) are prone to suffer insufficiency fractures due to secondary osteoporosis, as described in a series of three cases Visekruna M *et al.* 2008. Other risk factors are age per se with its implications such as malnutrition, decreased physical activity and an increased risk of falls from standing height Martin-Hunyadi C *et al.* 2000, Dolinak D. 2008. The following risk factors for fracture both from administrative and clinical data sources are as follows: prior fracture history; concomitant medications (glucocorticoids, thiazolidinediones, proton pump inhibitors, anticonvulsants, statins, HRT, SERMs, calcitonin), and co-morbid medical conditions (diabetes, rheumatoid arthritis, chronic kidney disease, malabsorption, errors of phosphate metabolism, joint replacement, vitamin D deficiency). **Oncology** Risk factor identified for fractures in patients with cancer is the underlying bone metastases. Bone metastases can produce osteolysis, osteogenesis or both. Purely osteolytic lesions can produce hypercalcaemia and increased concentration of bone matrix destruction markers (like urine hydroxyproline containing peptides). Usually, osteolytic lesions are associated with bone pain and in cases of increased bone destruction, fractures, are often reported at the metastatic determination site and pose a substantially increased burden of morbidity and even mortality in these patients. The long-term use of BPs (indicated for oncology and PMO) is thought to be the main risk factor for atypical fractures.
Preventability:	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 BP-treated patients who have sustained a femoral shaft fracture. Discontinuation of BP 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 BP 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 fracture. The optimal duration of BP treatment for osteoporosis has not been established. The need for continued treatment in osteoporosis should be re-evaluated periodically based on the benefits and risks of the BP on an individual patient basis. A temporary discontinuation after 3-5 years of bisphosphonate therapy may be appropriate in patients at low risk of fracture.
Impact on the risk-benefit balance of the product:	Femoral fractures have substantial negative impact on the patient's quality of life Valiyeva S *et al.* 2013. The benefit-risk balance for BPs is extremely favourable for up to 3 to 5 years. Due to evidence from epidemiological studies suggesting an increased risk of AFF with the long-term use of any BP, it is recommended to re-evaluate treatment based on the patient's benefits and risks of treatment particularly after 5 years..
Public health impact:	The absolute number of atypical femoral fractures reported with BPs is far lower than the number of osteoporotic fractures prevented.

Important identified risk: Hypocalcaemia	
Potential mechanism(s):	By specifically inhibiting osteoclast activity ibandronic acid leads to net gain in bone mass requiring (plasma) calcium.
Evidence source(s) and strength of evidence:	Mechanism of action: As other bisphosphonates, Bonviva may cause a transient decrease in serum calcium value [SmPC and Schlosser K. 1998].
Characterisation of the risk:	Under normal conditions, bisphosphonate-induced hypocalcaemia often subsides despite continued bisphosphonates therapy as increased parathyroid hormone (PTH) antagonises the effect of bisphosphonates in bone and conserves calcium by increasing tubular reabsorption of calcium in the kidneys and by stimulating the kidneys to produce 1,25-dihydroxyvitamin D. Symptomatic hypocalcaemia seems to be uncommon after oral bisphosphonate treatment and usually occurs weeks after the start of treatment. Frequency with 95% CI The risk was detected neither in the randomized, blinded trial population nor in the long-term exposure population.
Risk factors and risk groups:	Hyperparathyroidism, malignancy, thyroidectomy McHenry CR et al. 1994, Erbil Y *et al.* 2009, drug use such as lithium, chemotherapy, antibiotics, and BPs Maalouf NM *et al.* 2006, Tanvetyanon T *et al.* 2004, alcohol use Laitinen K *et al.* 1991, Vitamin D deficiency Nordin BE *et al.* 1989, renal failure Henley D *et al.* 2005.
Preventability:	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.

Impact on the risk-benefit balance of the product:	The impact on the patient quality of life can be considered low.
Public health impact:	None.

Important identified risk: Anaphylaxis	
Potential mechanism(s):	Anaphylaxis occurs in a previously sensitized person upon re- exposure to the sensitizing antigen (drug, anesthesia, insect stings, food, latex, exercise). An immediate IgE mediated immune response is the triggering factor. 20% of cases of anaphylaxis are idiopathic Sampson HA *et al.* 2006.
Evidence source(s) and strength of evidence:	Hypersensitivity reactions are labeled as rare Adverse Drug Reactions (ADRs) for ibandronic acid. Several preclinical tests and investigations were performed which raised no suspicion of ibandronic acid possessing antigenic properties. Skin sensitization tests were negative. No cases of 'anaphylaxis' associated with ibandronic acid were reported during clinical development program. However, the MAH identified that in some spontaneous reports the clinical manifestations of anaphylaxis (incl. fatal outcome) were present, and that the role of ibandronic acid could not be fully excluded. No signal was identified in the Atnahs Safety Database, nor in FDA AERS. From the literature, no publications were identified for the PMO and the oncology indications of ibandronic acid (and other bisphosphonates) in association with anaphylactic reactions and shock conditions.
Characterisation of the risk:	Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance Sampson HA *et al.* 2006. No reports of anaphylaxis potentially associated with ibandronic acid were observed in the clinical study database. Of the 50 events (47 reports) with a known outcome (n=34) reported spontaneously, most 30 (88.2%) recovered or were recovering, 4 (11.8%) of the 'anaphylaxis' reports had a fatal outcome (see DSR#1048486) Frequency with 95% CI The risk was not seen/observed in the randomized, blinded trial population nor in the long-term exposure population treated with ibandronic acid. **PMO** Data regarding the incidence of anaphylaxis are scarce. It is estimated that 1 in every 3000 inpatients in the US hospitals will suffer from an anaphylactic reaction with an estimated 1% resulting in death. A literature review revealed that anaphylaxis is not as rare as is generally believed and may affect between 1.2% and 15% of the US population, causing between 500-1000 deaths annually Neugut AI *et al.* 2001. A study conducted in

	Olmstead County, Minnesota revealed an annual incidence rate of anaphylaxis as 21 per 100,000 persons Yocum MW *et al.* 1999. The incidence rates in populations in the UK, Germany, and Denmark are estimated as 8.4, 9.8, and 3.2 per 100,000 person years, respectively Peng MM *et al.* 2004, Weiler JM. 1999. An investigation in the UK GPRD conducted in 2008 revealed that on average about 14 cases of anaphylaxis per 100,000 postmenopausal women with osteoporosis can be expected annually. The 95% confidence interval suggests that this could be as low as 5 cases or as high as 30 cases. The risk of anaphylaxis was higher amongst osteoporotic women compared with women in the general population (incidence rates: 13.7 vs 9.0 per 100,000 person years, respectively). However, this difference was not statistically significant (see Drug Safety Report No. 1048486). Until there are universally accepted diagnostic criteria, standardized coding, and reporting of anaphylaxis, the true incidence and lifetime prevalence will remain unknown Sampson HA *et al.* 2006. **Oncology** Five studies Burris H *et al.* 2004, Cobleigh MA *et al.* 1999, Esteva FJ *et al.* 2002, Fountzilas G *et al.* 2001, Burstein HJ *et al.* 2003 reported information on hypersensitivity or anaphylaxis. Of these, one study Burstein HJ *et al.* 2003 included early stage breast cancer patients and reported the following among patients treated with neoadjuvant paclitaxel and herceptin: Grade 1 (10%), Grade 2 (0%), Grade 3 (2.5%), Grade 4 (0%) and the following among patients treated with adjuvant doxorubicin and cyclophosphamide: Grade 1 (3%), Grade 2 (0%), Grade 3 (0%), Grade 4 (0%). The remaining four studies Burris H *et al.* 2004, Cobleigh MA *et al.* 1999, Esteva FJ *et al.* 2002, Fountzilas G *et al.* 2001 included metastatic breast cancer patients and reported a range in hypersensitivity and anaphylaxis from 0–38%.
Risk factors and risk groups:	As risk factors for anaphylaxis, a prior medical history positive for asthma, atopy, and/or (drug) hypersensitivity / allergy should be considered.
Preventability:	The basic approach to prevention is strict elimination and avoidance of offensive substances known to have allergic potential. Allergic reactions are unpredictable and dose- independent. Any drug can induce an immune response. Prophylactic corticosteroid and antihistamine therapy may be considered, although there is no data in the literature to suggest that pretreatment is effective for true anaphylactic reactions. Quick recognition and appropriate medical management of anaphylaxis is critical in avoiding fatal outcomes.
Impact on the risk-benefit balance of the product:	Anaphylaxis is a severe disorder that can be life-threatening without prompt treatment. However, symptoms usually improve with the right therapy.
Public health impact:	No impact, if at all then minimal impact.

Important potential risk: Renal dysfunction

<table>
<tr><td>Potential mechanism(s):</td><td>The mechanism of nephrotoxicity is an effect on the tubular cells in the kidney and is linked to the pharmacokinetic properties of each individual BP. The entry of a BP into the tubular cells is driven by three main pharmacokinetic parameters which are:
a plasma concentration-dependent uptake passive diffusion into tubular cells at the basolateral site,
plasma concentration profile of each individual BP related to infusion time and dose,
protein-binding: as only non-protein bound BP is taken up by renal tubular cells, the level of protein binding and the kinetics of dissociation of the drug-protein complex may modulate the cellular uptake.
While cellular uptake with the plasma concentration, excretion from tubular cells into the lumen can be saturated because it involves an active process, i.e. an energy dependent transport mechanism Lin JH et al. 1991, Joensuu TK. 2008, Kino I et al. 1999.

An imbalance between basolateral uptake and excretion into the lumen results in intracellular accumulation of BP and can result in cellular damage, as described for pamidronate and zoledronate Markowitz GS et al. 2001, Adami S et al. 1996.

There is evidence that the pathomechanism of cellular damage in the kidney is the same as the mechanism of osteoclast inhibition Luhe A et al. 2008. Therefore, the ratio between intracellular concentration and the cytotoxic potency of the BP is the resulting determinant for the risk of nephrotoxicity for BPs. As both the risk of intracellular accumulation and the potency differ among BPs, the renal safety profiles vary considerably between them Piccirillo JF et al. 2008.</td></tr>
<tr><td>Evidence source(s) and strength of evidence:</td><td>The earliest clinical use of a bisphosphonate (etidronate) was for the treatment of Paget's disease and dates back to 1971. Subsequently, with the use of intravenous bisphosphonates (etidronate, clodronate) for the treatment of malignant hypercalcemia due to osteolytic tumour-induced bone disease, several cases of renal failure were reported Bounameaux HM et al. 1983.</td></tr>
<tr><td>Characterisation of the risk:</td><td>Patterns of nephrotoxicity include toxic acute tubular necrosis and collapsing focal segmental glomerulosclerosis glomerulosclerosis depending on the bisphosphonate Piccirillo JF et al. 2008 and renal failure. Important factors which may increase renal toxicity of the IV bisphosphonates are higher dose, shorter infusion times or dose interval lower than recommended Bergner R et al. 2006. The total dose of the drug which has been administered during a long-term treatment may also play a role because of its probable cumulative effect Body JJ. 2006. The data support the conclusion that the half-life in plasma and soft tissues results in ibandronic acid being eliminated between doses, and that accumulation does not occur. Refer to renal toxicity [Part II: Module SII - Non-clinical part of the safety specification].

Frequency with 95% CI:

Randomized, blinded trial population
<table><tr><td>2.5 mg daily</td><td>150 mg monthly</td><td>3 mg IV</td></tr><tr><td>n / N (%)</td><td>n / N (%)</td><td>n / N (%)</td></tr><tr><td>5 / 860 (0.58%)</td><td>9 / 1,279 (0.70%)</td><td>1 / 469 (0.21%)</td></tr></table>Long Term Exposure Population</td></tr>
</table>

	150 mg monthly *3 mg IV* *n / N (%)* *n / N (%)* 12 / 1,464 (0.82%) 13 / 606 (2.15%) **Randomized, blinded trial population** *Relative risk (95% CI)* *Risk difference (95% CI)* *150 mg monthly* 1.21 (0.41, 3.60) 0.00 (0.01, -0.01) *3 mg IV* 0.37 (2.02, 3.13) -0.00 (-0.01, 0.00) **Randomized, blinded trial population** *2.5 mg daily* *150 mg monthly* *3 mg IV* *n / N (%)* *n / N (%)* *n / N (%)* 32 / 860 (3.72 %) 25 / 1,279 (1.95%) 14 / 469 (2.99%) **Long Term Exposure Population** *150 mg monthly* *3 mg IV* *n / N (%)* *n / N (%)* 35 / 1,464 (2.39%) 30 / 606 (4.95%) **Randomized, blinded trial population** Relative risk (95% CI) Risk Difference (95% CI) *150 mg monthly* 0.53 (0.31, 0.88) -0.02 (-0.03, -0.00) *3 mg IV* 0.80 (0.43, 1.49) -0.01 (-0.03, 0.01)
Risk factors and risk groups:	Pre-existing renal impairment, dehydration, nephrosclerosis, and hyperuricemia. Accidents, injuries, complications from surgery which result in kidneys being deprived of normal blood flow for extended period (e.g. heart bypass) Kes P *et al.* 2008, Smith R *et al.* 2007, Nowicki M *et al.* 2005. Drug overdoses - accidental or from chemical overloads of antibiotics or chemotherapy Miller A *et al.* 2009, Xu B *et al.* 2008. Diabetes mellitus Grinstead P. 2005. Hypertension Abdelwhab S *et al.* 2008, Havlucu Y *et al.* 2007. Genetic diseases Choukroun G *et al.* 1995. Obesity Ejerblad E *et al.* 2006. Family history McClellan WM *et al.* 2009, Joensuu TK. 2008. Overuse of common drugs (aspirin, ibuprofen, cocaine, acetaminophen) Perneger TV *et al.* 1994, Evans M *et al.* 2009, Fored CM *et al.* 2001.

Preventability:	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.
Impact on the risk-benefit balance of the product:	Regarding renal dysfunction, the impact on the patient quality of life can be significant, however the frequency of onset is low (>1%) and is heavily influenced by the presence of pre-existing risk factors. Overall, the risk-benefit balance of ibandronic acid remains extremely favourable.
Public health impact:	None.

Important potential risk: Atrial fibrillation

Potential mechanism(s):	The mechanism is not well understood. The high affinity of BPs binding to free calcium can be considered as a potential risk factor for AF. Based on the established effect of BPs in the treatment of hypocalcaemia, the impact on calcium homeostasis seems to be one of the most relevant factors to be discussed in connection to AF.
Evidence source(s) and strength of evidence:	On December 18, 2007, as part of the CHMP 'Class review of bisphosphonates and the potential risk of atrial fibrillation', the MAH was asked to provide the results of a review of cardiac arrhythmias and cerebrovascular disorders seen in clinical studies with ibandronic acid in PMO Black DM *et al.* 2007, Cummings SR *et al.* 2007 In the EMA fax dated June 20, 2008, the CHMP concluded that the risk of Atrial Fibrillation in association with bisphosphonate treatment remains low and that no specific risk minimization procedures were considered necessary for ibandronic acid at the moment.
Characterisation of the risk:	Overall, the incidence of atrial fibrillation was low in ibandronic acid trials, including the populations used in this analysis. Although the relative risk was numerically higher with the IV dose compared to the daily 2.5 mg dose, it was not statistically significant. Frequency with 95% CI: **Randomized, blinded trial population** *2.5 mg daily* *n / N (%)*: 3 / 860 (0.35%) *150 mg monthly* *n / N (%)*: 2 / 1,279 (0.16%) *3 mg IV* *n / N (%)*: 4 / 469 (0.85%) **Long Term Exposure Population** *150 mg monthly* *n / N (%)*: 6 / 1,464 (0.41%) *3 mg IV* *n / N (%)*: 9 / 606 (1.49%) **Randomized, blinded trial population** *150 mg monthly*: *Relative risk (95% CI)* 0.45 (0.08, 2.68); *Risk difference (95% CI)* -0.00 (-0.01, 0.00) *3 mg IV*: *Relative risk (95% CI)* 2.44 (0.55, 10.88); *Risk difference (95% CI)* 0.01 (-0.00, 0.01)
Risk factors and risk groups:	AF is the most common cardiac dysrhythmia seen in clinical practice, with a doubling in prevalence and incidence with each decade of life independent of known predisposing conditions Lip GY *et al.* 1995. Among others, hypertension and diabetes are reported as

	significant independent cardiovascular risk factors for AF after adjusting for age and other predisposing conditions. Being highly prevalent and common in the older population, hypertension accounts for more cases of AF than any other risk factor. Cardiac disorders such as coronary heart disease, valvular heart disease, heart failure, echocardiographic abnormalities or left ventricular hypertrophy have significant prevalence in the aging population and impose a substantial risk of AF (up to a 6- fold increase Lip GY *et al.* 1995. Other established risk factors responsible for AF are related to physiological stresses or metabolic disorders such as surgery, diabetes, thyrotoxicosis, insulin resistance or metabolic syndrome. These are common conditions in the elderly and in the population of patients participating in PMO studies. The presence of a history of AF at baseline represents an important risk factor for developing another episode of this condition in the near future. The exclusion criteria for these trials did not include any specific condition or disorder relevant to the risk factors listed above, except for medically significant conditions precluding participation in the trial. The overall incidence of AF in ibandronic acid studies was low. Importantly, ibandronic acid given either orally monthly or IV q3mo does not appear to be associated with an increased risk of AF. Overall, the number of patients reporting AF as an adverse event was low and no particular predisposing factor could be identified that would specifically expose patients to an increased risk for AF (beyond the known risk factors for AF) in association with treatment with ibandronic acid. Coronary artery disease/heart attack Bourke T *et al.* 2009, Novo G *et al.* 2008, Lip GY *et al.* 2008 Diabetes mellitus Lip GY *et al.* 2008, Iguchi Y *et al.* 2008, Schoonderwoerd BA *et al.* 2008 Hypertension Novo G *et al.* 2008, Schoonderwoerd BA *et al.* 2008 Smoking/drug or alcohol abuse Lip GY *et al.* 2008, Heeringa J *et al.* 2008 Obesity Schoonderwoerd BA *et al.* 2008 Family history of heart disease / congenital heart disorders Bedi M *et al.* 2006, Kato K *et al.* 2007, Juang JM *et al.* 2007 Age Lip GY *et al.* 2008, Iguchi Y *et al.* 2008, Medi C *et al.* 2007 Gender Lip GY *et al.* 2008, Iguchi Y *et al.* 2008.
Preventability:	Avoidance of correctable risk factors (e.g., calcium homeostasis).
Impact on the risk-benefit balance of the product:	The physical and psychological symptoms of atrial fibrillation impact negatively on the patients' quality of life Tapp DM *et al.* 2004, however the avoidance of correctable risk factors and low onset frequency limits the impact on the risk-benefit balance of the product.
Public health impact:	Minimal

SVII.3.2. Presentation of the missing information

Not applicable – no missing information safety concerns for product.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Osteonecrosis of the jaw Severe oesophageal irritation (only for oral IBN) Acute phase reaction Atypical fractures of long bones Hypocalcaemia Anaphylaxis
Important potential risks	Renal dysfunction Atrial Fibrillation
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are not
required for ibandronic acid. Routine pharmacovigilance activities are sufficient to monitor the safety profile of this product.

Targeted follow-up forms were in use for the following safety concerns within the previous EU RMP (dated 25 April 2016):

- Osteonecrosis of the jaw
- Atypical fractures of the femur

Targeted follow-up forms for "atypical fractures of the femur" have been in use since July 2013, whilst forms for "osteonecrosis of the jaw" have been in use since May 2012. Both risks are now classified as important identified risks, which are well characterised within the SmPC and followed up by routine pharmacovigilance activities including close monitoring via Periodic Safety Update Reports and Signal Detection. For these reasons, the MAH has proposed removal of these targeted follow-up forms from the pharmacovigilance plan and to monitor these risks as part of routine pharmacovigilance activities.

III.2 Additional pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the
product and detect any safety concerns. No activities are proposed that were imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk), specific obligations in the context of a conditional marketing authorisation or a

marketing authorisation under exceptional circumstances or required activities by the competent authority.

III.3 Summary Table of additional Pharmacovigilance activities

There are no on-going or planned safety studies included in the Pharmacovigilance Plan.

Part IV: Plans for post-authorisation efficacy studies

There are no post-authorization efficacy studies planned for ibandronic acid.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Osteonecrosis of the jaw (important identified risk)	Routine risk communication: *SmPC Section 4.2 (Bondronat 2mg, 6mg and Bonviva 3 mg solution for injection)* *SmPC Section 4.4 (all products concerned)* *SmPC Section 4.8 (all products concerned)* *PL Section 2 (all products concerned)* *PL Section 4 (all products concerned)* Routine risk minimization activities recommending specific clinical measures to address the risk: *In SmPC section 4.4:* *Recommendation to delay treatment in patients with unhealed open soft tissue lesions in the mouth.* *Recommendation for dental examination prior to treatment in patients with concomitant risk factors.* Other routine risk minimization measures beyond the Product information: *Pack size:* *Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC, sealed with aluminium foil) containing 1 or 3 tablets.* *Bondronat 50 mg film-coated tablets are supplied in blisters (aluminium) containing 7 tablets, which are presented as packs containing 28 or 84 tablets.* *Bondronat (IV) is supplied as packs containing 1, 5 and 10 vials (6 ml type I glass vial with a bromobutyl rubber stopper).* *Legal status: Prescription only medicine*
Severe oesophageal irritation (oral ibandronic acid only) (important identified risk)	Routine risk communication: *SmPC section 4.3 (all oral products concerned)* *SmPC section 4.4 (all oral products concerned)*

	PL Section 2 (all oral products concerned) *PL section 4 (all products concerned)* Routine risk minimization activities recommending specific clinical measures to address the risk: *In SmPC section 4.4:* *Recommendation for patients to comply with dosing instructions.* *Physicians to be alert of symptoms of oesophageal reaction and patients to discontinue treatment and seek medical attention.* Other routine risk minimization measures beyond the Product information: *Pack size:* *Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC, sealed with aluminium foil) containing 1 or 3 tablets.* *Bondronat 50 mg film-coated tablets are supplied in blisters (aluminium) containing 7 tablets, which are presented as packs containing 28 or 84 tablets.* *Legal status: Prescription only medicine*
Atypical fractures of long bones (important identified risk)	Routine risk communication: *SmPC section 4.4 (all products concerned)* *SmPC Section 4.8 (all products concerned)* *PL Section 2 (all oral products concerned)* *PL section 3 (all products concerned)* *PL section 4 (all products concerned)* Routine risk minimization activities recommending specific clinical measures to address the risk: *In SmPC section 4.2:* *Recommendation to re-evaluate treatment periodically based on the patient's benefits and risks of treatment particularly after 5 or more years of use.* *In SmPC section 4.4:* *Recommendation for discontinuation of treatment and examination of atypical fractures.* *Recommendation for patients to report symptoms of thigh, hip or groin pain to their doctor.*

	Other routine risk minimization measures beyond the Product information: *Pack size:* *Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC, sealed with aluminium foil) containing 1 or 3 tablets.* *Bondronat 50 mg film-coated tablets are supplied in blisters (aluminium) containing 7 tablets, which are presented as packs containing 28 or 84 tablets.* *Bondronat (IV) is supplied as packs containing 1, 5 and 10 vials (6 ml type I glass vial with a bromobutyl rubber stopper).* *Legal status: Prescription only medicine*
Acute Phase Reaction (important identified risk)	Routine risk communication: *SmPC section 4.8 (all products concerned)* *PL section 4 (all products concerned)* Routine risk minimization activities recommending specific clinical measures to address the risk: *In SmPC section 4.8:* *Notification that symptoms occur with first dose and usually resolve during continuing treatment with remedial measures.* Other routine risk minimization measures beyond the Product information: *Pack size:* *Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC, sealed with aluminium foil) containing 1 or 3 tablets.* *Bondronat 50 mg film-coated tablets are supplied in blisters (aluminium) containing 7 tablets, which are presented as packs containing 28 or 84 tablets.* *Bondronat (IV) is supplied as packs containing 1, 5 and 10 vials (6 ml type I glass vial with a bromobutyl rubber stopper).* *Legal status: Prescription only medicine*
Hypocalcaemia (important identified risk)	Routine risk communication: *SmPC section 4.3 (all products concerned)* *SmPC section 4.4 (all products concerned)* *SmPC section 4.8 (all products concerned)* *SmPC section 4.9 (all products concerned)* *PL section 4 (all products concerned)*

	Routine risk minimization activities recommending specific clinical measures to address the risk: *SmPC section 4.4:* *Recommendation for patients with hypocalcaemia to be corrected before initiating therapy and adequately supplemented with vitamin D and calcium during therapy.* Other routine risk minimization measures beyond the Product information: *Pack size:* *Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC, sealed with aluminium foil) containing 1 or 3 tablets.* *Bondronat 50 mg film-coated tablets are supplied in blisters (aluminium) containing 7 tablets, which are presented as packs containing 28 or 84 tablets.* *Bondronat (IV) is supplied as packs containing 1, 5 and 10 vials (6 ml type I glass vial with a bromobutyl rubber stopper).* *Legal status: Prescription only medicine*
Anaphylaxis (important identified risk)	Routine risk communication: *SmPC section 4.4 (all products concerned)* *SmPC section 4.8 (all products concerned)* *PL section 4 (all products concerned)* Routine risk minimization activities recommending specific clinical measures to address the risk: *In SmPC section 4.4:* *Recommendation that appropriate medical support should be readily available when injection is administered and discontinue if allergic reactions occur.* Other routine risk minimization measures beyond the Product information: *Pack size:* *Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC, sealed with aluminium foil) containing 1 or 3 tablets.* *Bondronat 50 mg film-coated tablets are supplied in blisters (aluminium) containing 7 tablets, which are presented as packs containing 28 or 84 tablets.* *Bondronat (IV) is supplied as packs containing 1, 5 and 10 vials (6 ml type I glass vial with a bromobutyl rubber stopper).* *Legal status: Prescription only medicine*

Renal dysfunction (important potential risk)	Routine risk communication: *SmPC section 4.2 (all products concerned)* *SmPC section 4.4 (all products concerned)* *PL section 2 (all products concerned)* *PL section 3 (all products concerned)* Routine risk minimization activities recommending specific clinical measures to address the risk: *SmPC section 4.2:* *Recommendation for patients with moderate or severe renal impairment to follow dosing recommendations.* *SmPC section 4.4:* *Recommendation for patients with risk factors for renal dysfunction to be regularly reviewed.* Other routine risk minimization measures beyond the Product information: *Pack size:* *Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC, sealed with aluminium foil) containing 1 or 3 tablets.* *Bondronat 50 mg film-coated tablets are supplied in blisters (aluminium) containing 7 tablets, which are presented as packs containing 28 or 84 tablets.* *Bondronat (IV) is supplied as packs containing 1, 5 and 10 vials (6 ml type I glass vial with a bromobutyl rubber stopper).* *Legal status: Prescription only medicine*
Atrial fibrillation (important potential risk)	Routine risk communication: *None* Routine risk minimization activities recommending specific clinical measures to address the risk: *None*

	Other routine risk minimization measures beyond the Product information: *Pack size:* *Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC, sealed with aluminium foil) containing 1 or 3 tablets.* *Bondronat 50 mg film-coated tablets are supplied in blisters (aluminium) containing 7 tablets, which are presented as packs containing 28 or 84 tablets.* *Bondronat (IV) is supplied as packs containing 1, 5 and 10 vials (6 ml type I glass vial with a bromobutyl rubber stopper).* *Legal status: Prescription only medicine*

V.2. Additional Risk Minimisation Measures

Additional Risk Minimisation Measure - Patient Reminder Card

Osteonecrosis of the jaw

Objectives:

The objective of the patient reminder card (PRC) is to provide greater clarity about the potential risk of ONJ and to inform patients of the need for timely and appropriate precautionary measures (i.e. seek medical attention early, inform dentists) to minimize the risk for ONJ as much as possible, also by keeping up a good routine care of teeth and the mouth.

Rationale for the additional risk minimisation activity:

The rationale of the use of the PRC is that with increased awareness the diagnosis of ONJ might be made more timely, and treatment of ONJ could be started earlier, including the discontinuation of Bonviva/Bondronat. Further by informing dentists ONJ may be avoided/prevented as a result of not performing invasive dental treatment, while the patient is under Bonviva/Bondronat treatment.

Target audience and planned distribution path:

Administration of Bonviva/Bondronat IV takes place in special settings, primarily infusion centers.

Provision of a patient reminder card (PRC) (for IBN IV patients only) to treating HCPs (physicians, nurses administering IBN IV) and subsequent hand-over to patients, to inform both the patient and healthcare professionals of the need for vigilance with respect to ONJ. The information emphasizes the need for good dental hygiene and timely and appropriate diagnosis. The PRC does not need to be supported by educational materials developed for patients and healthcare professionals as the awareness of ONJ is already quite high, and the relevant information is already covered in the Patient Reminder Card.

The distribution of PRCs to healthcare professionals by all EU affiliates will be initiated within six months of positive CHMP opinion via country-specific distribution channels. In accordance with the EU SmPC, physicians were mandated to provide the PRC to all IBN IV patients at the time of the treatment with Bonviva/Bondronat.

The individual affiliates will be responsible for dissemination of the PRCs, taking into account local treatment practices and regulatory considerations.

The patients on every visit need to show the card to all treating health care professionals, especially the dentist.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Note: As acknowledged, the risk of osteonecrosis (or death of bone tissue) in the jaw remains very low, the awareness of ONJ as a potential risk of bisphosphonate therapy with prescribers and dentists is already quite high, and it is unlikely that the proposed minimization measure will significantly increase that awareness.

Moreover, the ability to assess the effectiveness of the risk minimization measure would be very limited, as the rate of reporting of ONJ is already very low and the number of patients treated with IV Bonviva/Bondronat is also very low, decreasing, and further substituted with generic ibandronic acid (IBN).

Effectiveness will be assessed using both process and outcome indicators.

Process indicator:

The distribution of the PRC can be considered as a process indicator, and is documented within each scheduled PSUR (PBRER) for ibandronate, based on information received from our affiliates.

Outcome indicator:

Routine pharmacovigilance activities with comparisons between relative reporting rates of ONJ in relation to drug exposure at each PSUR.

Routine pharmacovigilance activities with comparisons between periods and geographies of relative reporting rates of ONJ cases in relation to drug exposure at each PSUR.

Note: The forecasted exposure of patients treated with IV Bondronat/Bonviva from beginning of 2017 to mid 2018 (DLP next EU PBRER) is estimated to be 4'000 and 60'000 patients respectively. With ONJ incidences of 1 to 100 (Bondronat - cancer) and 1 to 10'000 (Bonviva - osteoporosis), and a reporting of 1 in 10 cases of ONJ to the company, we are estimating receiving about 5-10 ONJ reports. Any interpretation of the outcome effectiveness measurements based on such small numbers will be highly questionable.

The occurrence of ONJ will be monitored through the MAH's routine pharmacovigilance system (including the use of guided questionnaires) and relative reporting rate in relation to drug exposure will be calculated to judge the success of the additional risk minimisation measure.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Osteonecrosis of the jaw	Routine risk minimisation measures: *SmPC Section 4.2 (IV products)* *SmPC Section 4.4 (all products)* *SmPC Section 4.8 (all products)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL Section 2 (all products) *PL Section 4 (all products)* Additional risk minimisation measures: *Patient reminder card*	*None*
Severe oesophageal irritation	Routine risk minimisation measures: *SmPC section 4.3 (oral products)* *SmPC section 4.4 (oral products)* *PL Section 2 (oral products)* *PL section 4 (oral products)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Atypical fractures of long bones	Routine risk minimisation measures: *SmPC section 4.2 (all products)* *SmPC section 4.4 (all products)* *SmPC Section 4.8 (all products)* *PL Section 2 (all products)* *PL section 3 (all products)* *PL section 4 (all products)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Acute Phase Reaction	Routine risk minimisation measures: *SmPC section 4.8 (all products)* *PL section 4 (all products)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Hypocalcaemia	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.3 (all products) *SmPC section 4.4 (all products)* *SmPC section 4.8 (all products)* *SmPC section 4.9 (all products)* *PL section 4 (all products)* Additional risk minimisation measures: *None*	*None* Additional pharmacovigilance activities: *None*
Anaphylaxis	Routine risk minimisation measures: *SmPC section 4.4 (all products)* *SmPC section 4.8 (all products)* *PL section 4 (all products)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Renal dysfunction	Routine risk minimisation measures: *SmPC section 4.2 (all products)* *SmPC section 4.4 (all products)* *PL section 2 (all products)* *PL section 3 (all products)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Atrial fibrillation	Routine risk minimisation measures: *None* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Part VI: Summary of the risk management plan

Summary of risk management plan for Bonviva/Bondronat (ibandronic acid)

This is a summary of the risk management plan (RMP) for Bonviva/Bondronat. The RMP details important risks of Bonviva/Bondronat, how these risks can be minimised, and how more information will be obtained about Bonviva/Bondronat's risks and uncertainties (missing information).

Bonviva/Bondronat's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Bonviva/Bondronat should be used.

This summary of the RMP for Bonviva/Bondronat should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Bonviva/Bondronat's RMP.

I. The medicine and what it is used for

Bonviva is indicated for:

- The treatment of osteoporosis in postmenopausal women at increased risk of fracture.
- A reduction in the risk of vertebral fracture has been demonstrated, efficacy on femoral neck fractures has not been established.

It contains ibandronic acid as the active substance and it is given orally or intravenously.

Bondronat is indicated in adults for:

- Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy of surgery) in patients with breast cancer and bone metastases.

It contains ibandronic acid as the active substance and it is given orally.

Further information about the evaluation of Bonviva/Bondronat's benefits can be found in Bonviva/Bondronat's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/bonviva and https://www.ema.europa.eu/en/medicines/human/EPAR/bondronat.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Bonviva/Bondronat, together with measures to minimise such risks and the proposed studies for learning more about Bonviva/Bondronat's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Bonviva/Bondronat, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Bonviva/Bondronat are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Bonviva/Bondronat. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Osteonecrosis of the jaw Severe oesophageal irritation (only for oral IBN) Acute phase reaction Atypical fractures of long bones Hypocalcaemia Anaphylaxis
Important potential risks	Renal dysfunction Atrial Fibrillation
Missing information	None

II.B Summary of important risks

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	Post-marketing experience.
Risk factors and risk groups	Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g. chemotherapy (including angiogenesis inhibitors Ruggiero SL *et al.* 2014 radiotherapy, corticosteroids), and co-morbid

	disorders (e.g. anemia, coagulopathy, infection, pre-existing dental disease, tobacco use and advanced age). Risk factors can be however categorized as follows Kanis JA *et al.* 2008. – Local (periodontal diseases, denture trauma (e.g. dental extraction), local malignancy, other concomitant oral diseases) – Demographic (age, race, cancer diagnosis, corticosteroid therapy, diabetes, smoking, alcohol use, poor oral hygiene, and chemotherapeutic drugs Tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily IV administered BPs. Many of these patients were also receiving chemotherapy and corticosteroids. ONJ has also been reported in patients with osteoporosis receiving oral BPs (in the osteoporosis setting). High doses clearly exceeding the IV and oral Bonviva dose for PMO are a risk factor of ONJ Goh SK *et al.* 2007, Odvina CV *et al.* 2005, Lee P *et al.* 2008. ONJ is more common in the oncology indication as compared to PMO indication. **Oncology** Data on the incidence of ONJ in oncology patients with bone metastases is available from denosumab phase III clinical trials. Incidence ranged from 1.3% - 2% in patients breast cancer, prostate cancer, multiple myeloma, and other cancers treated with denosumab or zoledronic acid Stopeck A *et al.* 2009, Fizazi K *et al.* 2010, Henry D *et al.* 2009. The incidence of ONJ among patients treated with bisphosphonates has varied widely among observational studies ranging from 1.1% -18.6% Walter C *et al.* 2009, Christodoulou C *et al.* 2009, McArthur HL *et al.* 2008. Among these, the two largest observational studies suggest a low incidence of ONJ. In a large medical chart review of 4019 cancer patients treated with IV pamidronate and/or zoledronic acid, the incidence of ONJ was 1.2% among 1338 breast cancer patients and 2.4% among 548 multiple myeloma patients (Hoff AO *et al.* 2008 also cited in Walter *et al.* 2009. No cases were observed in patients with other tumor types, which included renal cell, lung and prostate cancers. In a large medical chart review study at the Memorial Sloan-Kettering Cancer Center, the incidence of ONJ was 1.1% among 6561 cancer patients (breast cancer, multiple myeloma, prostate cancer, lung cancer and other) treated with IV pamidronate and/or zoledronic acid McArthur HL *et al.* 2008 . In summary, among IV bisphosphonate regimens, the incidence ONJ is infrequent as reported in phase III trials (<= 1% up to 1.4%). Observational studies report incidence

	proportions of 1.1-18.6% for bisphosphonate-containing regimens. The lack of standard definitions for ONJ, small sample sizes, and differences in risk factors (such as treatments, dental procedures) among patients may have led to variation between studies.
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.2 (IV products)* *SmPC Section 4.4 (all products)* *SmPC Section 4.8 (all products)* *PL Section 2 (all products)* *PL Section 4 (all products)* Additional risk minimisation measures: *Patient reminder card*

Important identified risk: Severe oesophageal irritation (only for oral IBN)	
Evidence for linking the risk to the medicine	A UK GRPD analysis revealed that subjects with osteoporosis not taking bisphosphonates had a higher incidence of upper GI tract events compared with sex-age matched non- osteoporosis group (incidence rates of 2.8% versus 1.8%) Cryer B *et al.* 2002, Van Staa T *et al.* 1997. Similarly, a United States Health Maintenance Organization (US HMO) study concluded that osteoporosis was a potential confounder for the alendronate-GI perforation, bleeding, and ulcer relationships Donahue JG *et al.* 2002. A member of the FDA's division of drug risk assessment submitted a letter to the editor of the New England Journal of Medicine Wysowski DK. 2009. Further, there was an FDA posting on potential signals associated with oral bisphosphonates as it pertains to esophageal cancer (Feb 4, 2009). http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm085925.htm. 2008. One small study of 154 breast cancer patients treated with either radiotherapy plus chemotherapy or radiotherapy alone found that 28% of patients treated with radiotherapy plus chemotherapy and 5% of patients treated with radiotherapy alone developed moderate or severe esophagitis/dysphagia Fiets WE *et al.* 2003.
Risk factors and risk groups	Risk factors of esophageal irritation are: Slow-release medications Lip GY *et al.* 1995, Bourke T *et al.* 2009, Novo G *et al.* 2008 and duodenal juice/acid reflux Lip GY *et al.* 2008, Iguchy Y *et al.* 2008.

Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3 (oral products)* *SmPC section 4.4 (oral products)* *PL Section 2 (oral products)* *PL section 4 (oral products)* Additional risk minimisation measures: *None*

Important identified risk: Acute phase reaction	
Evidence for linking the risk to the medicine	Intravenous nitrogen-containing bisphosphonates are known to cause an adverse event resembling the APR Adami S *et al.* 1987.
Risk factors and risk groups	No special risk groups or factors were investigated or identified.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8 (all products)* *PL section 4 (all products)* Additional risk minimisation measures: *None*

Important identified risk: Atypical fractures of long bones	
Evidence for linking the risk to the medicine	**Atypical femur fractures (AFF)** **PMO** Based on available literature, the occurrence of atypical femoral fractures for post-menopausal osteoporosis and/or over- suppression of bone turnover have been suggested to be associated with the prolonged use of bisphosphonates Visekruna M *et al.* 2008, Neviaser AS *et al.* 2008, Goh SK *et al.* 2007, Odvina CV *et al.* 2005, Lee P et al, 2008, Shane E *et al.* 2014. In EMA Responses dated 21 October 2010 EMA/CHMP/661040/2010, CHMP review under article 20 of regulation, the MAH concluded that a number of reports of subtrochanteric and diaphyseal femoral fractures with minimal or no trauma, and of non-femoral stress fractures, have been received for patients treated with ibandronate. **Oncology**

	After a thorough review of all available pre-clinical, clinical and published literature data, the MAH found no cases of atypical stress fracture associated with Bondronat (ibandronic acid) use in metastatic bone disease or tumor-related hypercalcaemia patients. For this reason, the MAH cannot provide any comments about any underlying pathophysiological mechanism(s) of atypical stress fractures in the case of Bondronat use in the label approved indications or provide any information regarding risk of atypical stress fractures or possible risk factors in this setting. **Atypical fractures at other sites** On 06 January 2021, The Pharmaceuticals and Medical Devices Agency (PMDA), Japan noted evidence supporting an association with ibandronic acid treatment with atypical fracture at sites other than the femur, and requested a product labelling update for Bonviva. As part of signal validation, a literature review suggested that atypical fractures of long bones, such as the ulna and tibia have also been reported in patients receiving long-term treatment Deguchi S *et al.* 2021; Handa K *et al.* 2020; Tan SH *et al.* 2015; Heo YMP *et al.* 2021; Asano Y *et al.* 2020; Moon J *et al.* 2013; Yam MG *et al.* 2017. These fractures occur after minimal, or no trauma and some patients experience prodromal pain prior to presenting with a completed fracture. The global safety database identified case reports of atypical fractures at other sites but was confounded by limited information.
Risk factors and risk groups	Atypical fractures of long bones appear to be more common in patients who have been exposed to long - term BPs, usually for more than 3 years (median treatment 7 years) Shane E *et al.* 2014. **PMO** Risk factors identified for fractures in patients with osteoporosis are female gender in combination with advanced age due to post-menopausal estrogen deficiency Metcalfe D. 2008. Patients with concomitant diseases requiring long-term glucocorticoid administration (e.g., rheumatoid arthritis) are prone to suffer insufficiency fractures due to secondary osteoporosis, as described in a series of three cases Visekruna M *et al.* 2008. Other risk factors are age per se with its implications such as malnutrition, decreased physical activity and an increased risk of falls from standing height Martin-Hunyadi C *et al.* 2000, Dolinak D. 2008. The following risk factors for fracture both from administrative and clinical data sources are as follows: prior fracture history; concomitant medications (glucocorticoids, thiazolidinediones, proton pump inhibitors, anticonvulsants, statins, HRT, SERMs, calcitonin), and co-morbid medical conditions (diabetes, rheumatoid arthritis, chronic kidney disease, malabsorption, errors of phosphate metabolism, joint replacement, vitamin D deficiency).

	Oncology Risk factor identified for fractures in patients with cancer is the underlying bone metastases. Bone metastases can produce osteolysis, osteogenesis or both. Purely osteolytic lesions can produce hypercalcaemia and increased concentration of bone matrix destruction markers (like urine hydroxyproline containing peptides). Usually, osteolytic lesions are associated with bone pain and in cases of increased bone destruction, fractures, are often reported at the metastatic determination site and pose a substantially increased burden of morbidity and even mortality in these patients. The long-term use of BPs (indicated for oncology and PMO) is thought to be the main risk factor for atypical fractures.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 (all products)* *SmPC section 4.4 (all products)* *SmPC Section 4.8 (all products)* *PL Section 2 (all products)* *PL section 3 (all products)* *PL section 4 (all products)* Additional risk minimisation measures: *None*

Important identified risk: Hypocalcaemia	
Evidence for linking the risk to the medicine	Mechanism of action: As other bisphosphonates, Bonviva may cause a transient decrease in serum calcium value [SmPC and Schlosser K. 1998].
Risk factors and risk groups	Hyperparathyroidism, malignancy, thyroidectomy McHenry CR et al. 1994, Erbil Y *et al.* 2009, drug use such as lithium, chemotherapy, antibiotics, and BPs Maalouf NM *et al.* 2006, Tanvetyanon T *et al.* 2004, alcohol use Laitinen K *et al.* 1991, Vitamin D deficiency Nordin BE *et al.* 1989, renal failure Henley D *et al.* 2005.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3 (all products)* *SmPC section 4.4 (all products)* *SmPC section 4.8 (all products)* *SmPC section 4.9 (all products)* *PL section 4 (all products)*

	Additional risk minimisation measures: *None*

Important identified risk: Anaphylaxis	
Evidence for linking the risk to the medicine	Hypersensitivity reactions are labeled as rare Adverse Drug Reactions (ADRs) for ibandronic acid. Several preclinical tests and investigations were performed which raised no suspicion of ibandronic acid possessing antigenic properties. Skin sensitization tests were negative. No cases of 'anaphylaxis' associated with ibandronic acid were reported during clinical development program. However, the MAH identified that in some spontaneous reports the clinical manifestations of anaphylaxis (incl. fatal outcome) were present, and that the role of ibandronic acid could not be fully excluded. No signal was identified in the Atnahs Safety Database, nor in FDA AERS. From the literature, no publications were identified for the PMO and the oncology indications of ibandronic acid (and other bisphosphonates) in association with anaphylactic reactions and shock conditions.
Risk factors and risk groups	As risk factors for anaphylaxis, a prior medical history positive for asthma, atopy, and/or (drug) hypersensitivity / allergy should be considered.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 (all products)* *SmPC section 4.8 (all products)* *PL section 4 (all products)* Additional risk minimisation measures: *None*

Important potential risk: Renal dysfunction	
Evidence for linking the risk to the medicine	The earliest clinical use of a bisphosphonate (etidronate) was for the treatment of Paget's disease and dates back to 1971. Subsequently, with the use of intravenous bisphosphonates (etidronate, clodronate) for the treatment of malignant hypercalcemia due to osteolytic tumour-induced bone disease, several cases of renal failure were reported Bounameaux HM *et al.* 1983.
Risk factors and risk groups	Pre-existing renal impairment, dehydration, nephrosclerosis, and hyperuricemia.

	Accidents, injuries, complications from surgery which result in kidneys being deprived of normal blood flow for extended period (e.g. heart bypass) Kes P *et al.* 2008, Smith R *et al.* 2007, Nowicki M *et al.* 2005. Drug overdoses - accidental or from chemical overloads of antibiotics or chemotherapy Miller A *et al.* 2009, Xu B *et al.* 2008. Diabetes mellitus Grinstead P. 2005. Hypertension Abdelwhab S *et al.* 2008, Havlucu Y *et al.* 2007. Genetic diseases Choukroun G *et al.* 1995. Obesity Ejerblad E *et al.* 2006. Family history McClellan WM *et al.* 2009, Joensuu TK. 2008. Overuse of common drugs (aspirin, ibuprofen, cocaine, acetaminophen) Perneger TV *et al.* 1994, Evans M *et al.* 2009, Fored CM *et al.* 2001.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 (all products)* *SmPC section 4.4 (all products)* *PL section 2 (all products)* *PL section 3 (all products)* Additional risk minimisation measures: *None*

Important potential risk: Atrial Fibrillation	
Evidence for linking the risk to the medicine	On December 18, 2007, as part of the CHMP 'Class review of bisphosphonates and the potential risk of atrial fibrillation', the MAH was asked to provide the results of a review of cardiac arrhythmias and cerebrovascular disorders seen in clinical studies with ibandronic acid in PMO Black DM *et al.* 2007, Cummings SR *et al.* 2007 In the EMA fax dated June 20, 2008, the CHMP concluded that the risk of Atrial Fibrillation in association with bisphosphonate treatment remains low and that no specific risk minimization procedures were considered necessary for ibandronic acid at the moment.
Risk factors and risk groups	AF is the most common cardiac dysrhythmia seen in clinical practice, with a doubling in prevalence and incidence with each decade of life independent of known predisposing conditions Lip GY *et al.* 1995. Among others, hypertension and diabetes are reported as significant independent cardiovascular risk factors for AF after adjusting for age and other predisposing conditions. Being highly prevalent and common in the older population, hypertension accounts for more cases of AF than any other risk factor. Cardiac disorders such as coronary heart disease, valvular heart disease, heart failure, echocardiographic

	abnormalities or left ventricular hypertrophy have significant prevalence in the aging population and impose a substantial risk of AF (up to a 6- fold increase Lip GY *et al.* 1995. Other established risk factors responsible for AF are related to physiological stresses or metabolic disorders such as surgery, diabetes, thyrotoxicosis, insulin resistance or metabolic syndrome. These are common conditions in the elderly and in the population of patients participating in PMO studies. The presence of a history of AF at baseline represents an important risk factor for developing another episode of this condition in the near future. The exclusion criteria for these trials did not include any specific condition or disorder relevant to the risk factors listed above, except for medically significant conditions precluding participation in the trial. The overall incidence of AF in ibandronic acid studies was low. Importantly, ibandronic acid given either orally monthly or IV q3mo does not appear to be associated with an increased risk of AF. Overall, the number of patients reporting AF as an adverse event was low and no particular predisposing factor could be identified that would specifically expose patients to an increased risk for AF (beyond the known risk factors for AF) in association with treatment with ibandronic acid. Coronary artery disease/heart attack Bourke T *et al.* 2009, Novo G *et al.* 2008, Lip GY *et al.* 2008 Diabetes mellitus Lip GY *et al.* 2008, Iguchi Y *et al.* 2008, Schoonderwoerd BA *et al.* 2008 Hypertension Novo G *et al.* 2008, Schoonderwoerd BA *et al.* 2008 Smoking/drug or alcohol abuse Lip GY *et al.* 2008, Heeringa J *et al.* 2008 Obesity Schoonderwoerd BA *et al.* 2008 Family history of heart disease / congenital heart disorders Bedi M *et al.* 2006, Kato K *et al.* 2007, Juang JM *et al.* 2007 Age Lip GY *et al.* 2008, Iguchi Y *et al.* 2008, Medi C *et al.* 2007 Gender Lip GY *et al.* 2008, Iguchi Y *et al.* 2008.
Risk minimisation measures	Routine risk minimisation measures: *None* Additional risk minimisation measures: *None*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Bonviva/Bondronat.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Bonviva/Bondronat.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

IBANDRONIC ACID (IBN) (BONVIVA®/BONDRONAT®) PATIENT REMINDER CARDS (PRCS)

BONVIVA PATIENT REMINDER CARD

This patient reminder card contains important safety information that you need to be aware of before and during treatment with ibandronic acid (Bonviva®).

Your doctor has recommended that you receive ibandronic acid, which is used to treat post-menopausal women with osteoporosis. This disease involves thinning and weakening of the bones so they may break more easily.

A side effect called osteonecrosis of the jaw (ONJ) (severe bone damage in the jaw) has been reported very rarely in patients receiving ibandronic acid 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 ONJ, there are some precautions you should take.

Before starting treatment:

Tell your doctor/nurse (health care professional) if you have any problems with your mouth or teeth, or if you wear dentures.

Your doctor may ask you to undergo a dental examination if you:

- were previously treated with another medication being a bisphosphonate
- are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- are a smoker
- have cancer
- have not had a dental check up for a long time
- have problems with your mouth or teeth

While being treated:

- You should maintain good oral hygiene, brush your teeth regularly 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 and tell your dentist that you are being treated with ibandronic acid (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.

Please read the package leaflet that comes with your medicine for further information.

Treatment start date and contact details

Date of first injection/infusion: ---------

Doctor's Name: ----------

Doctor's contact details: ----------

Dentist's Name: ----------

Dentist's contact details: ----------

Make sure you have a list of all your medicines when you see a health care professional.

Please talk to your doctor or nurse or dentist if you have any questions about the information in this card.

BONDRONAT PATIENT REMINDER CARD

This reminder card contains important safety information that you need to be aware of before and during treatment with ibandronic acid (Bondronat□) injections for cancer-related conditions.

Your doctor has recommended that you receive ibandronic acid, which is used in adults and prescribed to you if you have breast cancer that has spread to your bones, or if you have a raised calcium level in your blood due to a tumour. It helps to prevent your bones from breaking or your bones from getting weaker by reducing the amount of calcium that is lost from your bones.

A side effect called osteonecrosis of the jaw (ONJ) (severe bone damage in the jaw) has been reported very rarely in patients receiving ibandronic acid for cancer-related conditions. 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 ONJ, there are some precautions you should take.

Before starting treatment:

Tell your doctor/nurse (health care professional) if you have any problems with your mouth or teeth, or if you wear dentures.

Your doctor may ask you to undergo a dental examination if you:

- were previously treated with another medication being a bisphosphonate

- are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- are a smoker
- have not had a dental check up for a long time
- have problems with your mouth or teeth

While being treated:

- You should maintain good oral hygiene, brush your teeth regularly 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 and tell your dentist that you are being treated with ibandronic acid (Bondronat®).

- 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.

Please read the package leaflet that comes with your medicine for further information.

Treatment start date and contact details

Date of first injection/infusion: ---------

Doctor's Name: ----------

Doctor's contact details: ----------

Dentist's Name: ----------

Dentist's contact details: ----------

Make sure you have a list of all your medicines when you see a health care professional.

Please talk to your doctor or nurse or dentist if you have any questions about the information in this card.