Risk Management Plan Summary

Bonviva/Bondronat (Ibandronic Acid)

Marketing Authorisation Numbers:

Bondronat 2mg Concentrate Solution for Infusion (53626)

Bondronat 6mg Concentrate Solution for Infusion (57424)

Bondronat 50mg Film coated tablet (56360 01)

Bonviva 150mg Film coated tablet (57297)

Bonviva 3mg Solution for injection (57526)

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Marketing Authorization Holder:

Atnahs Pharma Switzerland AG

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Bonviva/Bondronat® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Bonviva/Bondronat ® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Atnahs Pharma Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Bonviva/Bondronat ®.

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, 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 – 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. 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. The incidence of ONJ among patients treated with bisphosphonates has varied widely among observational studies ranging from 1.1% -18.6%. 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 . 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. 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%). 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. A member of the FDA's division of drug risk assessment submitted a letter to the editor of the New England Journal of Medicine. Further, there was an FDA posting on potential signals associated with oral bisphosphonates as it pertains to esophageal cancer (Feb 4, 2009). 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.
Risk factors and risk groups	Risk factors of esophageal irritation are: Slow-release medications and duodenal juice/acid reflux.
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.

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. 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. 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). **PMO** Risk factors identified for fractures in patients with osteoporosis are female gender in combination with advanced age due to post- menopausal estrogen deficiency. Patients with concomitant diseases requiring long-term glucocorticoid administration (e.g., rheumatoid arthritis) are prone to suffer insufficiency fractures due to secondary osteoporosis. 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. 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 Section 4.4].
Risk factors and risk groups	Hyperparathyroidism, malignancy, thyroidectomy, drug use such as lithium, chemotherapy, antibiotics, and BPs, alcohol use, Vitamin D deficiency, renal failure.
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.
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). Drug overdoses - accidental or from chemical overloads of antibiotics or chemotherapy. Diabetes mellitus. Hypertension. Genetic diseases. Obesity. Family history. Overuse of common drugs (aspirin, ibuprofen, cocaine, acetaminophen).
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	In 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.

	In 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.
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. 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). 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. Diabetes mellitus. Hypertension. Smoking/drug or alcohol abuse. Obesity. Family history of heart disease / congenital heart disorders. Age. Sex.
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.