## VI.2 Elements for a public summary

### *VI.2.1 Overview of disease epidemiology*

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

Skeletal metastases are the most common malignancy of osseous tissue. Metastatic lesions are seen most often in the spine, femur, pelvis, ribs, sternum, and skull. Breast tumour is frequently spread to the skeletal system. More than 85% of bone metastases result from primary lesions in the breast, lung, or prostate. The occurrence of metastatic bone disease is highest in persons older than 40 years of age. These skeletal metastases cause great pain, increase the risk for fractures, and increase the disability of the patient with cancer.

Pathologic fractures occur in approximately 10% to 15% of persons with metastatic bone disease.

**Tumour-induced hypercalcaemia with or without metastases**

Hypercalcaemia is a fairly common metabolic emergency. Between 20-40% of patients with cancer develop hypercalcaemia at some point in their disease, and it is the most common serious electrolyte presenting in adults with malignancies. Increased blood level of calcium occurs in 10% to 20% of persons with metastatic bone disease.

**Osteoporosis in postmenopausal women and men at increased risk of fracture**

Due to its important prevalence worldwide, in post-menopausal women and in men is considered as a serious public health concern. Currently it is estimated that over 200 million people worldwide suffer from osteoporosis. Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe. At least 40% of these women and 15-30% of men will sustain one or more fragility fractures in their remaining lifetime. Ageing of populations worldwide will be responsible for a major increase of the incidence of osteoporosis in postmenopausal women.

### *VI.2.2 Summary of treatment benefits*

Based on the available data from clinical studies and clinical experience of several years, the following medicinal products represent an effective option in the treatment/prevention of concerned indications:

**Ibandronic acid Teva 50 mg film-coated tablets**

Ibandronic Acid Teva is used in adults and prescribed to you if you have breast cancer that has spread to your bones (called bone “metastases”).

- It helps to prevent your bones from breaking (fractures).
- It also helps to prevent other bone problems that may need surgery or radiotherapy.

Ibandronic Acid Teva works by reducing the amount of calcium that is lost from your bones. This helps to stop your bones from getting weaker.

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

Ibandronic Acid Teva is prescribed to you to treat postmenopausal osteoporosis because you have an increased risk of fractures. Osteoporosis is a thinning and weakening of the bones, which is common in women after the menopause. At the menopause, a woman’s ovaries stop producing the female

hormone, oestrogen, which helps to keep her skeleton healthy.

### *VI.2.3 Unknowns relating to treatment benefits*

Not applicable.

### *VI.2.4 Summary of safety concerns*

**IMPORTANT IDENTIFIED RISKS**

| Risk | What is known | Preventability |
|---|---|---|
| **Osteonecrosis of the jaw (ONJ)**<br><br>(Severe bone disease – bone damage, that affects the maxilla and the mandible) | A condition involving exposed bone in the mouth called "osteonecrosis of the jaw" has been reported.<br><br>Pain in the mouth, and/or the maxilla and the mandible, swelling or sores inside the mouth, numbness or a feeling of heaviness in the the maxilla and the mandible, or loosening of a tooth may occur. These could be signs of bone damage in the jaw (osteonecrosis) generally associated with delayed healing and infection, often following tooth extraction. | Patients may be advised to have a dental check-up before starting treatment with ibandronic acid.<br><br>If you are having dental treatment or surgery or know that you need some in the future, tell your dentist that you are being treated with ibandronic acid.<br><br>It is important to maintain good oral hygiene when being treated with ibandronic acid. The patients should have routine dental check-ups throughout the treatment and should contact doctor or dentist if experience any problems with mouth or teeth such as loose teeth, pain or swelling.<br><br>Talk to a nurse or a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:<br>• pain or sore in your mouth or jaw. |
| **Hypocalcaemia**<br><br>(Low calcium level in blood) | Low calcium levels in blood have been reported in some patients. | Low calcium level in the blood must be corrected before initiating therapy with ibandronic acid.<br><br>Other disturbances of bone and mineral metabolism (i.e. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting therapy with ibandronic acid.<br><br>Drug must not be used in patients with low calcium level in the blood. |
| **Severe oesophageal irritation**<br><br>(Adverse effects in gullet) | Irritation, inflammation or ulceration of the gullet (oesophagus – the tube that connects your mouth with your stomach) often with symptoms of chest pain, | Caution should be used:<br><br>- In patients who have any swallowing or digestive problems<br><br>- In patients who cannot stay in the upright position for at least 30 minutes after taking |

| Risk | What is known | Preventability |
|---|---|---|
| | heartburn, or difficulty or pain upon swallowing may occur, especially if patients do not drink a full glass of water and/or if they lie down less than 30 minutes after taking ibandronic acid. | the tablet<br><br>- If ibandronic acid is given to patients with active or recent oesophageal or upper gastrointestinal problems (including known Barrett's oesophagus - a condition associated with changes in the cells that line the lower oesophagus).<br><br>Prescribers should pay attention to the dosing instructions and be alert to any signs and symptoms of possible oesophageal reaction. The patients should be instructed to look for medical help if they develop symptoms of oesophageal irritation such as difficulty or pain on swallowing, chest pain or new/worsened heartburn.<br><br>Drug must be used according to the instructions.<br><br>**The tablet must be swallowed whole and not sucked or chewed. To safely deliver the tablet to the stomach, it is to be taken while in an upright position with a glass of plain water (≥120 ml). Patients should not lie down for 30 minutes after taking the tablet.** |
| **Acute phase reaction**<br><br>(A group of physiologic changes that occur shortly after the onset of an infection or other inflammatory process) | Flu-like symptoms (including fever, chills, bone pain and aching muscles) have been reported. These symptoms usually disappear within a couple of hours or days. | If you get any side effects, talk to your doctor or pharmacist. |
| **Anaphylaxis**<br><br>(Potentially life threatening allergic reaction) | Patients allergic (hypersensitive) to ibandronic acid or to any of the excipients should not take this medicinal product.<br><br>The following adverse reactions have been reported: allergic and skin reactions, including swelling of the face, lips, tongue | Do not take ibandronic acid:<br>- if you are allergic (hypersensitive) to ibandronic acid<br><br>Talk to a nurse or a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:<br>• rash, itching, swelling of your face, lips, tongue and throat, with difficulty breathing. You may be having an allergic reaction to the medicine<br>• problems with breathing. |

| Risk | What is known | Preventability |
|---|---|---|
| | and/or throat, generalised rash, hives, severe skin reactions. | |

**IMPORTANT POTENTIAL RISKS**

| Risk | What is known |
|---|---|
| **Atypical femoral fracture**<br>(Unusual fracture in the upper thigh bone) | New pain, weakness or discomfort in thigh, hip or groin have been reported with ibandronic acid. These may be early signs of a possible unusual fracture of the thigh bone. |
| **Atrial fibrillation** | Atrial fibrillation has been reported with some bisphosphonates (drug class effect). The potential of developing atrial fibrillation with ibandronic acid is not known. |
| **Renal dysfunction** | Take special care if you have kidney problems. Your doctor may adjust your dose and duration of intravenous infusion if you have kidney problems.<br>Changes in blood test results such as creatinine have been reported. |

**MISSING INFORMATION**

None

### *VI.2.5 Summary of additional risk minimisation measures by safety concern*

No additional risk minimisation measures are proposed.

### *VI.2.6 Planned post authorisation development plan (if applicable)*

Not applicable.

### *VI.2.7 Summary of changes to the risk management plan over time*

Major changes done to the Risk Management Plan over time are presented in the following table:

| RMP Version | Date | Safety concerns | Comment |
|---|---|---|---|
| version 1.0, For bisphos-phonates | 26 Sep 2011 | Identified risks for oral formulations: osteonecrosis of the jaw (ONJ), hypocalaemia and, oesophageal adverse effects<br><br>Potential risks for oral formulations: atypical femoral fracture, atrial fibrillation, hypersensitivity reactions and | A combined RMP for the 4 bisphosphonates (INN's alendronic acid, clonodronic acid, pamidronic acid, ibandronic acid).<br>The RMP was issued due to the Commission Implementing Decision of 13 July 2011 concerning the Article 31 referral for bisphosphonates requiring that the MAHs should submit/update the RMPs to reflect |

| RMP Version | Date | Safety concerns | Comment |
|---|---|---|---|
| | | ocular adverse events.<br><br>Important missing information: use during pregnancy and lactation and use in patients below 18 years of age | "atypical femoral fractures" as a potential risk. |
| Version 2.0, For ibandronic acid | 20 Apr 2012 | Identified risks: osteonecrosis of the jaw (ONJ), hypocalaemia and, oesophageal adverse effects<br><br>Potential risks: atypical femoral fracture, atrial fibrillation, hypersensitivity reactions, ocular adverse events, acute phase reaction (intermittent oral therapy and intravenous therapy) and renal impairment/ renal failure (parenteral formulations).<br><br>Important missing information: use during pregnancy and lactation, use in patients below 18 years of age and patients with severe renal impairment. | Version was updated to RMP for ibandronic acid only; oral and parenteral formulations.<br>Sections updated to include the exact wording specified in Article 31 referral regarding "atypical femoral fractures", as per abbreviated core RMP for bisphosphonates; changes in sections 2.2, 2.3, 3.1 and 5.<br><br>In comparison with RMP for all bisphosphonates, the following safety concerns were added in RMP v2.0:<br>• important potential risks: acute phase reaction (intermittent oral therapy and intravenous therapy) and renal impairment/ renal failure (parenteral formulations)<br>• important missing information: patients with severe renal impairment |
| Version 2.1, For ibandronic acid | 14 Aug 2013 | Identified risks: osteonecrosis of the jaw (ONJ), hypocalaemia and, oesophageal adverse effects, atypical femoral fracture, hypersensitivity reactions, ocular adverse events<br><br>Potential risks: atrial fibrillation, acute phase reaction (intermittent oral therapy and intravenous therapy) and renal impairment/ renal failure (parenteral formulations)<br><br>Important missing information: use during pregnancy and lactation, use in patients below 18 years of age and patients with severe renal impairment. | No change in safety concerns;<br>However, based on GVP Module V definitions of safety concerns, atypical femoral fracture, hypersensitivity reactions, and ocular adverse events were upgraded into identified risks since these adverse reactions are included in section 4.8 in the SmPCs.<br><br>All sections have been re-organized and/or updated as compared to version 2.0 based on GVP template for generics; major changes in format are in Part V and Part VI.<br><br>In addition, follow-up questionnaire on atypical femoral fracture is added in Annex 7. |
| Version 2.2, For ibandronic acid for tablets and parenteral formulations | 10 Sep 2013 | Identified risks: osteonecrosis of the jaw (ONJ), hypocalaemia and, oesophageal adverse effects, atypical femoral fracture, hypersensitivity reactions, ocular adverse events, acute phase reaction (intermittent oral therapy and intravenous therapy) | No change in safety concerns;<br>However, based on the request from the Dutch Medicines Evaluation Board acute phase reaction (intermittent oral therapy and intravenous therapy) was upgraded into identified risk. |

| RMP Version | Date | Safety concerns | Comment |
|---|---|---|---|
| | | Potential risks: atrial fibrillation, and renal impairment/ renal failure (parenteral formulations)<br><br>Missing information: use during pregnancy and lactation, use in patients below 18 years of age and patients with severe renal impairment. | |
| Version 3.0, For ibandronic acid tablets | 31 May 2016 | Identified risks: osteonecrosis of the jaw (ONJ), osteonecrosis of the external auditory canal, hypocalcaemia, severe oesophageal irritation, acute phase reaction, anaphylaxis<br><br>Potential risks: atypical femoral fractures, atrial fibrillation, renal dysfunction<br><br>Missing information: none. | RMP v3.0 is applicable for ibandronic acid tablets only.<br>Safety concerns have been changed to be in line with the safety concerns of the reference product as recommended in ibandronic acid FRARs (NL/H/1831/001-002/R/001; NL/H/1832/001/R/001; NL/H/1833/001-002/R/001) dated 17 April 2015. |
| Version 3.1, for ibandronic acid tablets | 25 July 2016 | Identified risks: osteonecrosis of the jaw (ONJ), hypocalcaemia, severe oesophageal irritation, acute phase reaction, anaphylaxis<br><br>Potential risks: atypical femoral fractures, atrial fibrillation, renal dysfunction<br><br>Missing information: none. | Osteonecrosis of the external auditory canal was removed from the list of safety concerns as recommended in ibandronic acid PVAR (NL/H/1831/001-002/IB/013, NL/H/1832/001/IB/010, NL/H/1833/001-002/010) dated 04 July 2016. |