5.2 Part VI.2 Elements for a Public Summary

5.2.1 Part VI.2.1 Overview of disease epidemiology

Tumor induced hypercalcemia

Hypercalcemia is too much calcium in the blood. Hypercalcemia is relatively common in patients with cancer, occurring in approximately 20 to 30 percent of cases [Stewart 2005]. It is the most common cause of hypercalcemia in the inpatient setting. It occurs in patients with both solid tumors and hematologic malignancies. It occurs more often with some cancers like breast, myeloma, lung, kidney, and head and neck cancers than in others like lymphoma. It also occurs more often when the cancer is at an advanced stage and is most commonly associated with widespread bone metastases.

Osteolytic bone metastases

Metastases leading to destruction of bones (osteolytic) account for approximately 20 percent of cases of hypercalcemia of malignancy. Induction of local bone destruction by tumor cells is common with some solid tumors that are metastatic to bone and with multiple myeloma, but it is less common with lymphoma and leukemia. Breast Cancer is the most often seen cause of bone metastases. The bone destruction observed in osteolytic metastases is primarily mediated by special cells in the bones (osteoclasts) and is not a direct effect of tumor cells. Instead, tumors produce many factors that stimulate such cell production and action leading to bone loss.

Myelomatosis

Multiple myeloma (MM) is a debilitating malignancy. First described in 1848, MM is characterized by a proliferation of malignant white blood cells and a subsequent overabundance certain proteins in the blood produced by these cells. An intriguing feature of MM is that the antibody-forming cells (i.e. plasma cells) are malignant and therefore, may cause unusual manifestations. The proliferation of plasma cells in MM may interfere with the normal production of blood cells, resulting in decreased numbers of healthy white blood cells, red blood cells and platelets. The cells may cause soft-tissue masses or lytic lesions in the skeleton (bones). Feared complications of MM are bone pain, elevated calcium in the blood, renal failure, and spinal cord compression. The American Cancer Society (ACS) estimates that about 26,850 new cases of MM (14,090 in men and 12,760 in women) will be diagnosed in 2015. In the United States, the lifetime risk of getting MM is one in 143 (0.7%). About 11,240 deaths from MM (6,240 in men and 5,000 in women) are expected to occur in 2015.[American Cancer Society 2015]

5.2.2 Part VI.2.2 Summary of treatment benefits

Patients with advanced malignancy involving bone are at significant risk, such as the occurrence of tumor-induced hypercalcemia (TIH), which is an elevated level of calcium and the risk for bone morbidity. TIH can be a life-threatening complication of malignancy. Bone metastases from solid tumors and osteolytic bone disease in multiple myeloma are associated with considerable skeletal (bone) morbidity, including severe pain, pathologic fracture, the requirement for radiation or surgery to bone (to relieve pain, treat or prevent fracture), nerve root and spinal cord compression. These skeletal complications substantially reduce the quality of life for patients with bone metastases.

Pamidronate has demonstrated efficacy in the treatment of TIH and the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced elevated calcium level) in patients with advanced malignancies involving bones.

Bisphosphonates have become a standard of care in patients with multiple myeloma and breast cancer, and are recommended in ASCO clinical practice guidelines for these malignancies [ASCO 2007, ASCO 2011].

5.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There are no clinical data from the use of pamidronate in pregnant women. Embryonal/fetal toxicities were seen in studies in pregnant rats. Due to extremely limited experience and the potential of pamidronate to have an important impact on bone mineralization, breastfeeding during the therapy should be avoided. There is a lack of data on safety and efficacy in children and adolescents as well as in patients with severe hepatic impairment.

5.2.4 Part VI.2.4 Summary of safety concerns

Table 5-5 Important identified risks

Risk	What is known	Preventability
Destruction or death of jawbone (Osteonecrosis of the jaw)	Destruction or death of jawbone, so called osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered a class of drugs, so called bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates like pamidronate.	Patients should tell their doctor before taking pamidronate if they have or have had pain, swelling or numbness of the jaw, loosening of a tooth or a 'heavy jaw feeling'. A dental examination with appropriate preventive dentistry should be considered prior to treatment with oral bisphosphonates in patients with poor dental status. During bisphosphonate treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.
Impairment of the kidney function (Renal function impairment)	Uncommonly (may affect up to 1 in 100 people), acute worsening of kidney function and very rarely (may affect up to 1 in 10,000 people) changes in kidney function, including worsening of an existing kidney problem, e.g. blood were observed with use of Pamidronate.	Patients should tell their doctor before taking pamidronate if they have or have ever had any kidney problems.
Low calcium in blood (Hypocalcemia)	Pamidronate lowers calcium level in blood. Low calcium level in blood can lead to undesired effects like sensory disorders (paresthesia), tonic spasm (tetanus) and fall in blood pressure (hypotension).	Calcium level in blood should be monitored and corrected to normal values if too low, prior to administration of pamidronate.
Irregular heart rhythm (Atrial fibrillation)	Irregular heart rhythm (atrial fibrillation) has been seen in up to 1 in 10 patients receiving pamidronate. It is currently unclear whether pamidronate causes this irregular heart rhythm.	You should report to your doctor if you experience irregular heart rhythm during treatment with pamidronate.
Interaction with calcitonin (medicine for high calcium levels)	Other medicines for high calcium levels such as calcitonin can interfere with your treatment.	Tell the doctor or nurse if you are taking other medicines for high calcium levels such as calcitonin.
Interaction with nephrotoxic drugs (drugs which may affect the kidneys)	Other medicines that may affect the kidneys (Your doctor or nurse will know which drugs these are.) can interfere with your treatment.	Tell the doctor or nurse if you are taking other medicines that may affect the kidneys

Risk	What is known	Preventability
Interaction with thalidomide (used to treat some cancers)	Thalidomide can interfere with your treatment.	Tell the doctor or nurse if you are taking thalidomide

Table 5-6 Important potential risks

Risk	What is known
Unusual thighbone fracture (Atypical femur fracture)	Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Patients should contact their doctor if they experience pain, weakness or discomfort in their thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone. If you start to get pain, weakness or discomfort in your thigh, hip or groin you should tell you doctor immediately as these can be early signs.
Worsening of heart disease (Deterioration of cardiac disease)	Worsening of heart function (breathlessness, pulmonary congestion) or congestion of influx before the heart (accumulation of water in tissue) due to hyperhydration may affect up to 1 in 10,000 patients treated with pamidronate (very rare side effect). Talk to your doctor before receiving pamidronate if you have a history of heart disease.
Worsening of low levels of red blood cells, white blood cells or reduction in blood platelets (Deterioration of anemia, leukopenia or thrombocytopenia)	Reduction of red and white blood cells and blood platelets may affect up to 1 in 10 patients treated with pamidronate (common side effect). Talk to your doctor before receiving pamidronate if you have low levels of red blood cells, white blood cells or a reduction in blood platelets, which increases the risk of bleeding or bruising, you should have regular hematology assessments.

Table 5-7 Missing information

Risk	What is known
Use in pediatric patients (children)	The number of children and adolescents exposed to pamidronate is limited. Safety and efficacy in this patient group has not been established.
Fertility, pregnancy and lactation (breast-feeding)	Do not use pamidronate if you are pregnant or you are breast-feeding an infant. The number of pregnant or breast-feeding women exposed to pamidronate is limited. Safety and efficacy in this patient group has not been established. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You must use highly effective contraception during treatment with pamidronate. Your doctor should not prescribe pamidronate to you except in cases of life-threatening hypercalcemia. Breast-feeding during therapy with pamidronate should be avoided. There are no data available if pamidronate has any impact on fertility.

Risk	What is known
Use in patients with severe renal impairment (impairment of the kidneys)	There is limited experience in patients with severe impairment of the kidneys. Pamidronate should not be administered to patients with severe impairment of the kidneys (creatinine clearance <30 mL/min) unless in cases of life-threatening tumor-induced hypercalcemia where the benefit outweighs the potential risk.
Use in patients with hepatic (liver) insufficiency	The number of patients with severe hepatic impairment exposed to pamidronate is limited. Safety and efficacy in this patient group has not been established.

5.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures). Full details on these conditions and the key elements of any educational material can be found in Annex 11 "Mock-up of proposed additional risk minimization measures"; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimization measures are for the following risk:

Table 5-8 Summary of risk minimization measures for Osteonecrosis of the jaw

Risk minimization measure(s)
Summary description of main additional risk minimization measures: Patient reminder card Objective and rationale: To alert patients on the risk of Osteonecrosis of the jaw Proposed action: The patient reminder card contains the following key messages: • Need to inform the doctor/nurse about any problems with the mouth or teeth, prior to starting the treatment with pamidronic acid • Need to go for a dental examination if the patients were previously treated with bisphosphonates, are taking medicines called corticosteroids, are smokers, have cancer, or have not had a dental check-up for a long time. While being treated, • Need to maintain good oral hygiene and receive routine dental check-ups • Need to inform doctor in case of planning to have dental surgeries as well as inform dentist about being treated with pamidronic acid.

5.2.6 Part VI.2.6 Planned post authorization development plan

None

5.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	07 Jul 2015	Newly added important identified risks: • Osteonecrosis of the jaw • Bone, joint and/or muscle pain • Renal toxicity • Hypocalcemia • Injection site reaction Newly added missing information: • Use in pediatric patients • Use during pregnancy and lactation • Use in patients with severe hepatic impairment	Review and update 3 years after first RMP approval
2.1	10 Dec 2015		According to the requirements in the MRP Type IB variation Preliminary Variation Assessment Report on Pamidronat “Hexal” Concentrate for solution for infusion, 15mg/1ml in DK/H/0498/001/IB/019 dated 18 Nov 2015 the following was updated:
		N/A	Inclusion of Part II Module SV
		Important identified risk “Renal toxicity”	modified to “Renal function impairment”
		“Atypical femur fracture”	moved from important identified to important potential risk
		“Atrial fibrillation”, “Interaction with calcitonin”, “Interaction with nephrotoxic drugs”, “Interaction with thalidomide”	included as new important identified risks
		“Deterioration of cardiac disease”, “Deterioration of anemia, leukopenia or thrombocytopenia”	included as new important potential risks
			To establish more alignment to the originator RMP, the following was updated in addition:
		Important identified risks “Bone,	deleted

Version	Date	Safety Concerns	Comment
		joint and/or muscle pain", "Injection site reactions"	
		Missing information "Use during pregnancy and lactation" and "Use in patients with severe hepatic impairment"	amended to "Fertility, pregnancy and lactation" and "Use in patients with hepatic insufficiency"
		Missing information "Use in patients with severe renal impairment"	added
		Important identified risk "Osteonecrosis of the jaw"	According to PRAC Lead Member State PSUR preliminary assessment report on Pamidronate (PSUSA00002269201505) dated 31 May 2015, a patient reminder card was included as additional risk minimization measure in all applicable RMP parts.