VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pamidronate disodium belongs to a group of medicines called bisphosphonates which can help to regulate the amount of calcium in the blood. High blood calcium levels (hypercalcaemia) occur in a number of conditions, including some types of cancer. Often, hypercalcaemia is caused by the release of calcium from bones. The drug sticks to bones and helps to reduce the release of calcium into the blood.

Patients with spread of disease of breast cancer to bone are dominated by osteolytic lesions and in some patients with cancer results in bone loss throughout the body associated with bone pain. Pamidronate disodium is used to treat osteolytic lesions and relieve bone pain in patients with spread of bone diseases associated with breast cancer and disease of bone marrow (multiple myeloma). Pamidronate disodium is also used to treat Paget's disease which results in a change in bone structure.

VI.2.2 Summary of treatment benefits

Experimental studies have demonstrated that pamidronate inhibits tumour-induced osteolysis when given prior to or at the time of inoculation or transplantation with tumour cells. Biochemical changes reflecting the inhibitory effect of pamidronate disodium on tumour-induced hypercalcaemia, are characterised by a decrease in serum calcium and phosphate and secondarily by decreases in urinary excretion of calcium, phosphate and hydroxyproline.

Hypercalcaemia can lead to depletion in the volume of extracellular fluid and a reduction in the glomerular filtration rate (GFR). By controlling hypercalcaemia, pamidronate disodium improves GFR and lowers elevated serum creatinine levels in most patients.

Clinical trials in patients with breast cancers treated by chemotherapy and predominantly lytic bone metastases or with multiple myeloma stage III with associated osteolytic lesions showed that pamidronate disodium prevented or delayed skeletal-related events (hypercalcaemia, fractures, radiation therapy, surgery to bone, spinal cord compression) and decreased bone pain).

VI.2.3 Unknowns relating to treatment benefits

The safety of pamidronate disodium has not been studied in patients with severe liver impairment, severe kidney impairment, races other than Caucasians, on fertility, in pregnant and breast-feeding females and in children and adolescents.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Renal function impairment	A condition in which the kidneys lose the ability to remove waste and balance fluids. It is rarely reported with the Pamidronic Disodium.	Physician should be informed before using Pamidronic Disodium. The physician should do a blood test to check your kidney function while taking Pamidronic Disodium.
Osteonecrosis of the jaw	Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates, including pamidronic acid. Most cases have been in cancer patients treated with intravenous bisphosphonates undergoing dental procedures. Some cases have occurred in patients with postmenopausal osteoporosis treated with either oral or intravenous bisphosphonates. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may worsen the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ.	A routine oral examination should be performed by the prescriber prior to initiation of bisphosphonate treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, pre-existing dental disease or infection, anemia, coagulopathy). While on treatment, patients with concomitant risk factors should avoid invasive dental procedures if possible.
Hypocalcemia	The medicine is used to help lower high levels of calcium in the blood caused by tumours, and reduce bone loss, which may occur in patients with certain types of cancer, for example breast cancer or multiple myeloma. Reduced levels of calcium in the blood (hypocalcaemia), sometimes leading to muscle cramps, dry skin and burning	Physician should be informed in case of reduced levels of calcium. Adequate calcium and vitamin D supplements will be prescribed to patients with pre-existing hypocalcaemia.

Risk	What is known	Preventability
	sensation maybe experienced by patients receiving Pamidronic Disodium.	
Atrial fibrillation	Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving Pamidronic Disodium. It is currently unclear whether Pamidronic Disodium this irregular heart rhythm.	Physician should be informed regarding irregular heart rhythm while taking Pamidronic Disodium.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Atypical femoral fracture	Unusual fracture of the thigh bone, particularly in patients on long-term treatment for osteoporosis, may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.

Missing information

Risk	What is known
Races other than Caucasian	Non-Proposed
Paediatric patients	There is no clinical experience in the paediatric and adolescent (<18 years old) population. Therefore it not recommended for the use in children.
Fertility, pregnancy and lactation	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. There are no clinical data on the use of Pamidronatdinatrium Hospira concentrate for solution for infusion during pregnancy. Animal studies have shown harmful effects on the offspring (skeletal alterations). The potential risk for humans is unknown. If you are pregnant, you should not be treated with pamidronate unless absolutely necessary. Breast-feeding is not recommended whilst being treated with Pamidronatdinatrium Hospira concentrate for solution for infusion
Patients with severe renal impairment	Pamidronate disodium should not be administered to patients with severe renal impairment unless in case of life-threatening high levels of calcium induced by tumour.

Risk	What is known
Patients with hepatic insufficiency	Pamidronate disodium has not been studied in patients with severe hepatic impairment, therefore no specific recommendations can be given for this patient population.

VI.2.5 Summary of risk minimisation 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 minimising 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 minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Pamidronate Disodium can be found in the Pamidronate Disodium's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Following Pharmacovigilance Risk Assessment Committee (PRAC) recommendation and the Position of the Co-ordination Group for Mutual Recognition and Decentralised Procedures for human use (Procedure Number EMA/CMDh/37409/2016), a patient reminder card will be implemented to alert patients about the identified risk for Osteonecrosis of Jaw. How it is implemented in each country will depend upon agreement between the manufacturer and the national authorities.

Safety concern in lay terms (medical term)

Risk minimisation measure – Osteonecrosis of Jaw
Objective and rationale: The objectives of the patient alert card are: To provide patients with a constant reminder that can be carried in a purse or wallet of the more important safety concerns associated with Pamidronate Disodium treatment. To remind the patient to tell his/her doctor of important symptoms that may suggest that he/she has developed osteonecrosis of Jaw. To remind the patients to tell his/her doctor/nurse (health care professional) if they have any problems with your mouth or teeth before starting treatment with Pamidronate Disodium.

Risk minimisation measure – Osteonecrosis of Jaw
Summary description of main additional risk minimisation measures: Patients must be given a patient alert card highlighting the following risks: • If he/she experiences any problems with their mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, while during therapy or after completion of therapy as these could be signs of osteonecrosis of the jaw. • To maintain good oral hygiene, brush their teeth regularly and receive routine dental check-ups. • If he/she is under dental treatment or will undergo dental surgery (e.g. tooth extractions) to inform their doctor and tell your dentist that you are being treated with Pamidronate Disodium.

VI.2.6 Planned post authorisation development plan

There are no planned post authorisation development plans for Pamidronate Disodium.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
V 2.0		Identified Risks Potential Risks Missing information	RMP updated in the new EU RMP generic template (EMA/465933/2013 Rev 1) Part I - Additional information added to the section 4.2 Posology and method of administration of the SmPC following Pharmacovigilance Risk Assessment Committee (PRAC) recommendation and the Position of the Co-ordination Group for Mutual Recognition and Decentralised Procedures for human use (Procedure Number EMA/CMDh/37409/2016). Part II – Summary of safety concerns amended in line with the innovator as recommended by final PSUR assessment report (Procedure No: PSUSA00002269201505) adopted by CMDh position and agreed by the consensus on the 27-Jan-2016. Important identified risks: Renal function impairment, Osteonecrosis of the jaw, Hypocalcemia and Atrial fibrillation Missing Information: Races other than

Version	Date	Safety Concerns	Comment
			Caucasian, Pediatric patients, Fertility, pregnancy and lactation, Patients with severe renal impairment and Patients with hepatic insufficiency. Part III – Pharmacovigilance plan section updated taking into consideration the updated identified/potential risks and missing information (as recommended by final PSUR assessment report (Procedure No: PSUSA00002269201505) adopted by CMDh position and agreed by the consensus on the 27-Jan-2016). Part V – Risk minimization measures section updated taking into consideration the updated identified/potential risks and missing information ((as recommended by final PSUR assessment report (Procedure No: PSUSA00002269201505) adopted by CMDh position and agreed by the consensus on the 27-Jan-2016). Included details on the Risk Minimisation Measure for osteonecrosis of the Jaw (patient alert card) and information on checking its effectiveness as per Pharmacovigilance Risk Assessment Committee (PRAC) recommendation and the Position of the Co-ordination Group for Mutual Recognition and Decentralised Procedures for human use (Procedure Number EMA/CMDh/37409/2016. Part VI – Section updated taking into consideration the updated identified/potential risks and missing information (as recommended by final PSUR assessment report (Procedure No: PSUSA00002269201505) adopted by CMDh position and agreed by the consensus on the 27-Jan-2016).
V 1.0	20-March-2012	Atypical femoral fracture as an potential identified risk	• Initial RMP