Paminject 3 mg/ml, concentrate for solution for infusion

25.2.2016, Version V3.0

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

Paminject 3 mg/ml, concentrate for solution for infusion

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).

VI.2.2 Summary of treatment benefits

Paminject 3 mg/ml is a medicine that affects bone structure and uptake or release of minerals from the bones.

Paminject 3 mg/ml belongs to the drug group of bisphosphonates.

It is used in the treatment of the following diseases associated with an increased activity of bone dissolving cells:

- high blood calcium levels (hypercalcaemia) caused by tumours
- sites of bone injury (osteolytic lesions) in patients with bone metastases associated with breast cancer
- a bone marrow tumour, which is due to enhanced production of certain immune cells (multiple myeloma stage III)

Paminject 3 mg/ml is used to lower the calcium level in blood. The calcium level in blood may be increased in several different conditions, for example in association with some types of cancer. If high blood calcium levels are not treated it can cause symptoms such as feeling sick (nausea), tiredness and confusion.

Generally high blood calcium levels are due to the release of calcium from the bone. Paminject 3 mg/ml affects the bone dissolving cells so that the amount of calcium released to the blood is reduced. In some patients with cancer the medicine is used for the treatment of bone disease.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of pamidronate disodium has not been studied in patients with severe liver impairment, severe kidney impairment and in children and adolescents.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Unusual fracture of the thigh bone (Atypical femoral fractures)	Unusual fracture of the thigh bone particularly in patients on long-term treatment 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.
Kidney function impeirment (Renal function impairment)	Bisphosphonates, including pamidronate disodium, have been associated with kidney toxicity established as deterioration of kidney function and potential kidney failure. Degenerative or inflammatory kidney disorders leading to impaired kidney function may affect up to 1 in 100 people. Worsening of kidney function in patients with multiple myeloma or pre-existing kidney disease may affect up to 1 in 10,000 people	Your kidney function should be periodically checked, especially if you receive Paminject 3 mg/ml frequently over a prolonged period of time, and if you have a pre-existing kidney disease or you are prone to kidney problems (e.g. because of multiple myeloma and/or high blood calcium levels caused by tumours). If your kidney function gets worse during Paminject 3 mg/ml therapy, the infusion must be stopped.
Death of the jaw bone (Osteonecrosis of the jaw)	A severe injury of the jaw bone (osteonecrosis) has been reported in patients with cancer receiving treatment regimens including pamidronate disodium. Most of these cases were associated with dental procedures such as tooth extraction.	You should inform the dentist before any dental treatment or surgery and you should consider a dental examination with appropriate advice (e.g. maintaining good oral hygiene, amendment of poorly fitting dentures, smoking reduction) before starting treatment with Paminject 3 mg/ml. While on treatment, you should avoid invasive dental procedures if possible and should have regular dental check-ups. If you develop bone death of the jaw (symptoms might be pain or swelling of the gums and/or jaw, numbness of the jaw, the jaw feeling heavy, or toothloss) while on Paminject 3 mg/ml therapy, dental surgery may make the condition worse. Your doctor

		should make an individual benefit/risk assessment.
Calcium level too low (Hypocalcaemia)	Low blood calcium levels with symptoms such as numbness, tingling and/or muscle cramps are rare.	Please tell your doctor if you are taking other medicines for the treatment of high blood calcium levels, as the use of these other medicines with Paminject 3 mg/ml may lead to very low blood calcium level which may cause symptoms such as numbness, tingling or cramps. Tell your doctor, before you are given Paminject 3 mg/ml, if you suffer from calcium or vitamin D deficiency (for example owing to your diet or as a result of digestive problems). If you have undergone thyroid surgery, you may be more prone than usual to develop too low calcium blood levels.
Abnormal heart rhythm (Atrial fibrillation)	Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving pamidronate disodium. The frequency cannot be estimated.	You should report to your doctor if you experience irregular heart rhythm during treatment with pamidronate.
Scarring of the lung tissue (Interstitial lung disease)	Scarring of the lung tissue has been reported in less than 1 in 10,000 patients receiving pamidronate disodium.	You should report to your doctor if you experience dry cough or shortness of breath at exertion.
Fluid build-up in lungs (Adult respiratory distress syndrome)	Fluid build-up in lungs, leading to oxygen deprivation, has been reported in less than 1 in 10,000 patients receiving pamidronate disodium.	You should report to your doctor if you experience shortness of breat, low blood pressure, confusion or rapid breathing..

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
None	NA

Missing information

Risk	What is known (Including reason why it is considered a potential risk)
Use in children and adolescents (Pediatric patients)	There is not enough clinical experience available for the use of pamidronate disodium in children and adolescents (< 18 years).
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. You should not use Paminject 3 mg/ml during pregnancy except in cases of life-threatening high blood calcium levels. Women of child-bearing potential must use highly effective contraception during treatment. Do not breast-feed your baby during therapy with Paminject 3 mg/ml. No data on fertility are available.
Patients with severe kidney impairment	Because there is only limited clinical experience in patients with severe kidney impairment, no dose recommendations for this patient population can be made.
Patients with liver insufficiency	Clinical data in patients with severe hepatic impairment is not available. Pamidronate should be administered to this patient population with caution.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures).

These additional risk minimisation measures are for the following risks:

Death of the jaw bone (osteonecrosis of the jaw)

Risk minimisation measure(s)
Although the risk may be well known for the prescribers, further awareness on such risk is needed for the patients. Thus, a patient reminder card as an additional risk minimisation measure is to be implemented.
• Patient reminder card – further patient awareness of jaw bone death risk

VI.2.6 Planned post authorisation development plan

No post-authorisation studies have been imposed or are planned.

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

Version	Date	Safety Concerns	Comment
V01	2012-Nov-05	Important potential risk: • Atypical femoral fractures	none
V02	2013-Aug-30	The following risks were added as important identified risks: • Anaemia, thrombocytopenia, lymphocytopenia, leukopenia • Cardiac failure (left ventricular failure or congestive heart failure) • Reactions at the infusion site • Hypersensitivity • Hypocalcaemia • Osteonecrosis of the jaw (ONJ) • Musculoskeletal pain (transient bone pain, arthralgia, myalgia) • Convulsions • Renal toxicity (deterioration of renal function, renal failure) The following risks were added as important potential risks: • Atrial fibrillation • Off label use (in adults and children) The following risks were added as missing information: • Use in children and adolescents	none
V3.0	2016-Feb-25	Atypical femoral fractures and atrial fibrillation have been reclassified as important identified risks. The following risks were added as important identified risks: • Interstitial lung disease • Adult respiratory distress syndrome The following risks were added as missing information: • Fertility, pregnancy and lactation • Patients with severe renal impairment • Patients with hepatic insufficiency	Not yet approved

Version	Date	Safety Concerns	Comment
		The following risks have been deleted: • Anaemia, thrombocytopenia, lymphocytopenia, leukopenia • Cardiac failure (left ventricular failure or congestive heart failure) • Reactions at the infusion site • Hypersensitivity • Musculoskeletal pain (transient bone pain, arthralgia, myalgia) • Convulsions • Off label use (in adults and children)	