

## **Part VI: Summary of the risk management plan**

### **Summary of risk management plan for MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 %.**

This is a summary of the risk management plan (RMP) for MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 %.

The RMP details important risks of MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 %, how these risks can be minimised, and how more information will be obtained about MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 %'s risks and uncertainties (missing information).

MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 %'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 % should be used.

Important new concerns or changes to the current ones will be included in updates of MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 % 's RMP.

### **I. The medicine and what it is used for**

MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 % is proposed to be authorized for use in adults for the treatment of tumour-associated osteolysis, multiple myeloma, primary hyperparathyroidism, prevention and treatment of post-menopausal osteoporosis. The product contains clodronate disodium and lidocaine hydrochloride as active substances and it is administered for intramuscular use.

### **II. Risks associated with the medicine and activities to minimise or further characterise the risks**

Important risks of MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 %, together with measures to minimize such risks and the proposed studies for learning more about MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 %'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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 % is not yet available, it is listed under 'missing information' below

## ***II.A List of important risks and missing information***

Important risks of MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 %, are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 MADRAS 100 mg /3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg /4 mL solution for intramuscular use with lidocaine 1 %. 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).

<b>List of important risks and missing information</b>	
<b>Important identified risks</b>	Osteonecrosis of jaw (for clodronate)
	Renal impairment (for clodronate)
	Cardiac toxicity (for lidocaine)
	Nervous system toxicity (for lidocaine)
<b>Important potential risks</b>	Transaminases level increase (for clodronate)
	Ocular and visual disturbances (for clodronate)
	Osteonecrosis of external auditory canal (for clodronate)
	Atypical femoral fracture (for clodronate)
	Familial malignant hyperthermia crisis in patients at risk (for lidocaine)

List of important risks and missing information	
Missing information	Data on fertility, pregnancy and lactation (for clodronate)

## II.B Summary of important risks

### Safety concerns related to clodronate

Important identified risks	
Osteonecrosis of jaw	
Evidence for linking the risk to the medicine	The information about osteonecrosis of jaw is presented in literature and in the SmPC and PIL.
Risk factors and risk groups	<p>Risk group is represented by patients treated bisphosphonates.</p> <p>Patients treated for long time, patients who underwent dental surgery and patients exposed to bisphosphonates for oral or intravenous administration and chemotherapy, radiotherapy and steroids are groups with higher risk factors for osteonecrosis of jaw. A poor oral hygiene is an additional risk factor for this risk.</p>
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>A warning concerning the risk of osteonecrosis of jaw for oncologic patients treated with systemic bisphosphonates that undergo dental extraction or suffer from infection is reported in paragraph 4.4 of SmPC and related PIL section.</p> <p>Paragraph 4.4 of SmPC and related PIL section, also include a warning concerning patient undergone chemotherapy, radiotherapy and steroid treatment or with poor hygiene, that should consider dental visit and prophylactic dental measure before starting therapy with bisphosphonates. Dental surgery should be avoided and, if it is necessary, treatment with bisphosphonates should be discontinued.</p> <p><i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>

<b>Renal impairment</b>	
Evidence for linking the risk to the medicine	The information about the risk of renal impairment is presented in literature and in the SmPC and PIL.
Risk factors and risk groups	<p>Patients with pre-existing renal diseases are at increased risk. Concomitant intake of NSAIDs could be a risk factor for renal impairment or worsening of existing renal dysfunction.</p> <p>In fact NSAIDs have been associated with acute kidney injury in the general population and with progression of disease in those patients with chronic kidney disease. Concomitant administration of bisphosphonates, including clodronate, could have an additive effect on renal function.</p>
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>Section 4.2 of the SmPC includes a specific scheduling of dose of MADRAS 003 when it is administered to patients suffering from renal insufficiency. Posology scheme is based on renal functionality and clearance of creatinine of patients.</p> <p>Section 4.4 of SmPC includes a recommendation to monitor renal function during treatment with MADRAS . Appropriate hydration should be maintained during clodronate treatment. Related PIL section states that the patient should inform the physician if he/she is affected by renal insufficiency.</p> <p>Section 4.5 of SmPC and related PIL section state that there is an increased risk of renal insufficiency when MADRAS is taken concomitantly with NSAIDs.</p> <p>Section 4.8 of SmPC and related PIL section include renal insufficiency and severe renal damage among the ADRs.</p> <p><i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>
<b>Potential risks</b>	

<b>Transaminases level increase</b>	
Evidence for linking the risk to the medicine	The information about potential increase of transaminases is presented in literature and in SmPC and PIL.
Risk factors and risk groups	There are no particular risk factors and risk groups.
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>Recommendations about the monitoring of hepatic function and transaminase levels are reported in the SmPC sections 4.4.</p> <p>Paragraph 4.8 of SmPC and related PIL section report transaminases level increase among ADRs.<i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>
<b>Ocular and visual disturbances</b>	
Evidence for linking the risk to the medicine	The information about the risk of ocular and visual disturbances is presented in literature and in SmPC and PIL.
Risk factors and risk groups	There is not a particular risk group, however comorbidities, polypharmacy and intravenous administration could be considered as risk factors for ocular side effects.
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>Recommendations to suspend the treatment and seek physician advice if any visual alteration occur is included in SmPC sections 4.8 and related PIL section.<i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>
<b>Osteonecrosis of external auditory canal</b>	
Evidence for linking the risk to the medicine	The information about the risk of osteonecrosis of external auditory canal is presented in literature and in SmPC and PIL.

Risk factors and risk groups	Risk group is represented by patients treated with clodronate for long-term therapy (2 years or longer) or treated concomitantly with radiotherapy, chemotherapy and steroids. Elderly patients are also a risk group due to their vulnerability to osteoporosis. Infection or trauma are also classified as risk factors for osteonecrosis of external auditory canal.
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>Recommendations to consider osteonecrosis of external auditory canal in patients showing chronic ear infection or auditory disturbance is reported in SmPC paragraph 4.4 and in section 4 of PIL.</p> <p>Risk of osteonecrosis of external auditory canal is reported in SmPC paragraph 4.8.</p> <p><i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>
<b>Atypical femoral fracture</b>	
Evidence for linking the risk to the medicine	The information about the risk of atypical femoral fracture is presented in literature and in SmPC and PIL.
Risk factors and risk groups	Risk group is represented by patients treated with clodronate and bisphosphonates with long term therapies for osteoporosis and malignancies. The risk factors also include history of low-energy fractures, use of glucocorticoids for more than 6 months, active rheumatoid arthritis and low serum level of vitamin D (Saita et al 2015).
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>Section 4.4 of SmPC and related PIL section state that a withdrawal of therapy should be considered in patients with atypical femoral fractures and medical evaluation should be sought. Patients should be informed to report to their physician every pain or discomfort localized to their hips, thighs and groin.</p>

	<p>Risk of atypical femoral fractures is reported in paragraph 4.8 of SmPC and related PIL section.</p> <p><i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>
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#### Missing Information

#### Data on fertility, pregnancy and lactation

Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>The use of product is not recommended in pregnant women and women in child-bearing age without appropriate contraception due to lack of data of potential toxic effect on foetus.</p> <p>Breastfeeding should be discontinued during clodronate and bisphosphonates treatment due to lack of data concerning safety for child.</p> <p><i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>
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#### Safety concerns related to lidocaine

Important identified risks	
Cardiac toxicity	
Evidence for linking the risk to the medicine	The information about the risk of cardiac toxicity is presented in literature and in SmPC and PIL.
Risk factors and risk groups	Risk group is represented by patients affected by Adam-Stokes syndrome, Wolff-Parkinson White syndrome (atrial fibrillation), bradycardia and cardiac insufficiency and hepatic impairment treated with lidocaine.

	<p>Risk factors include accidental intravascular injections and concomitant administration of propranolol, cimetidine and digitalis-containing medicinal products.</p>
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>The product is contraindicated in patients suffering for heart conduction diseases, such as Adam Stokes syndrome, Wolff-Parkinson White syndrome (atrial fibrillation), severe sinoatrial, atrioventricular or intraventricular block and acute heart failure (SmPC section 4.3 and related PL section).</p> <p>Since cardiac toxicity is a consequence of increased plasmatic level of lidocaine a careful control of the patient is required in the presence of severe hepatic diseases, as reported in paragraph 4.4 of SmPC. The patients should be monitored up to 30 minutes after the product administration to verify that no lidocaine-related toxicity occurs.</p> <p>A specific warning to avoid the accidental intravascular administration of lidocaine due to the increased risk of lidocaine-induced toxicity is also reported in paragraph 4.4 of SmPC.</p> <p>Interactions which can increase the risk of cardiac toxicity are reported in section 4.5 of the product SmPC <i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p>.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>
<b>Nervous system toxicity</b>	
Evidence for linking the risk to the medicine	<p>The information about the risk of nervous system toxicity is presented in literature and in SmPC and PIL.</p>



Risk factors and risk groups	<p>Risk group is represented by patients affected by severe hepatic impairment treated with lidocaine.</p> <p>Risk factors include accidental intravascular injections and concomitant administration of propranolol and cimetidine.</p>
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>Due to possible increased risk of toxicity-related to the high plasmatic concentration of lidocaine, a warning to perform an accurate control of the patient in the presence of severe hepatic diseases as reported in SmPC sections 4.4 and related PIL section.</p> <p>A specific warning concerning increased risk of nervous system toxicity induced by intravascular injection of lidocaine is reported in SmPC, paragraph 4.4, and related PIL section.</p> <p>Interactions which can increase the risk of lidocaine toxicity, are reported in section 4.5 of the product SmPC.</p> <p><i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>
<b><u>Potential risks</u></b>	
<b>Familial malignant hyperthermia crisis</b>	
Evidence for linking the risk to the medicine	The information about the risk of familial malignant hyperthermia crisis in patients at risk is presented in literature and in SmPC and PIL.
Risk factors and risk groups	Risk group is represented by patients affected by familial malignant hyperthermia exposed to volatile anaesthetics.
Risk minimization measures	<p><u>Routine risk minimization measures:</u></p> <p>The warning about the risk of familial malignant hyperthermia crisis after administration of local</p>

	<p>anesthetics, such as lidocaine, is included in paragraph 4.4 of SmPC and related PIL section.</p> <p><i>Other routine risk minimization measures beyond the Product Information</i></p> <p>Legal status of medicine: Prescription only medicine.</p> <p><u>Additional risk minimization measures:</u></p> <p>Not applicable.</p>
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## ***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 MADRAS 100 mg / 3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg / 4 mL solution for intramuscular use with lidocaine 1 %.

### **II.C.2 Other studies in post-authorisation development plan**

There are no studies required for MADRAS 100 mg / 3,3 mL solution for intramuscular use with lidocaine 1 % and MADRAS 200 mg / 4 mL solution for intramuscular use with lidocaine 1 %.