VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Since Dotarem® is not a medicinal product, but a diagnostic agent which is used to image a large number of organs, this section is not applicable.

VI.2.2 Summary of treatment benefits

Dotarem® is used to enhance the contrast of the images obtained during MRI examinations. This contrast enhancement improves the examination of some areas of the body.

Dotarem® is used for contrast enhancement to improve the visualisation and delineation of:

- defects (lesions) in brain, spinal cord and adjacent tissue;
- defects (lesions) in liver, kidneys, pancreas, pelvis, lungs, heart, breast and musculoskeletal system;
- defects (lesions) and narrowing (stenosis) in arteries, except in coronary arteries (adults only).

Dotarem® has been used for a long time in a range of MRI procedures and for a wide variety of patients (both sexes, and from children to the elderly). The efficacy and safety profile of Dotarem® have been demonstrated in 50 clinical trials comprising 2,822 patients and in 10 studies conducted after marketing of Dotarem® comprising more than 180,000 patients.

In addition to the clinical trials performed before Dotarem® was marketed, efficacy has been re-confirmed in more recent studies, including studies in Germany and in Japan.

In the study in Germany, using Dotarem® enabled a diagnosis to be made in almost all patients (99.7%) and was equally good in men and women. However, the quality of the scans made using Dotarem® dropped as patients' weight increased (as measured by body mass index). Other reasons for poor quality, aside from technical problems with the scan, included patients moving while being scanned or having metal objects in their body.

In the study in Japan, physicians considered Dotarem® 'very effective' or 'effective' in the majority of patients (1075 (31.4%) and 2335 cases (68.1%), respectively, of 3426 cases in total). So, the overall effectiveness was similar to the results obtained in the trials conducted prior to approval.

VI.2.3 Unknowns relating to treatment benefits

The efficacy of Dotarem® as a contrast enhancing agent in the approved indications has been adequately evaluated in the completed clinical study program, and no additional PAES are required to support the use of Dotarem® as described in the approved SmPCs.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Nephrogenic Systemic Fibrosis (NSF)	NSF is a rare and serious syndrome that involves a build-up of connective tissue in the skin, joints, eyes, and internal organs. As a consequence, it can lead to shortening of muscles and joint immobility, and in some cases inability to walk. The skin becomes thickened and woody in texture, starting in the	NSF can be avoided by avoiding GBCA use in renally impaired patients. Therefore, patients should be screened for impaired renal function prior to administration of gadoteric acid. This is especially important for elderly patients. The risk of NSF is also higher in some patient groups, like patients in the

Risk	What is known	Preventability
	legs and arms, sometimes involving the trunk, but the face is always spared. Other organs may become affected later including the lungs, liver, muscles, and heart, in some cases leading to a fatal outcome. NSF occurs as a result of GBCA used for MRI imaging. It essentially never occurs in patients with normal renal function, but is observed in around 0.4% patients on long-term haemodialysis and almost 10% patients with end-stage renal insufficiency who are not on dialysis. There are different categories of NSF-risk for GBCAs: high, medium and low risk. Gadoteric acid is considered a low risk GBCA.	perioperative liver transplantation phase and with immature renal function (children < 1 year). The benefit of GBCA enhanced imaging may still outweigh the risk even in some renally impaired patients. Haemodialysis shortly after gadoteric acid administration may be useful at removing gadoteric acid from the body for patients who are already on dialysis. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.
Convulsions	Patients with low seizure threshold can be at risk of convulsions after Dotarem® injection. However, the risk if very rare and can be minimized by a good compliance of anti-epileptic drugs in epileptic patients.	For patients with a low threshold for seizures, during imaging with Dotarem® injection preventive measures should be taken, e.g. close monitoring and access to all equipment and drugs necessary to counter any convulsions which may occur.
Anaphylaxis	As with other gadolinium containing contrast media hypersensitivity reactions can occur, including life-threatening. Hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non allergic. They can be either immediate (less than 60 minutes), or delayed (up to 7 days). Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, can occur after even the first dose of the product, and are often	Before any contrast medium is injected, the patient should be questioned for a history of allergy (e.g. seafood allergy, hay fever, hives), sensitivity to contrast media and bronchial asthma. In patients with these conditions premedication with antihistamines and/or glucocorticoids may be considered. During the examination, supervision by a physician is necessary. If hypersensitivity reactions occur, administration of the contrast medium must be

Risk	What is known	Preventability
	unpredictable. As known from the use of iodinated contrast media, hypersensitivity reactions can be aggravated in patients on beta-blockers, and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta-agonists.	discontinued immediately and - if necessary - specific therapy started. Appropriate drugs, an endotracheal tube and a respirator should be ready at hand.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
- Accumulation and retention of gadolinium in the brain - Gadolinium accumulation in organs and tissues other than brain tissues	Gadolinium Based Contrast Agents (GBCAs) are generally completely eliminated from the body via urine within several hours. However, several articles published in international scientific journals suggest that gadolinium accumulate in skin, bone and, in specific regions of the brain (globus pallidus and dentate nucleus) of patients with normal renal function receiving multiple administrations of GBCAs. To date, the accumulation varies according to the GBCA administered and the renal status of the patients.

Missing information

Missing information	What is known
Use of Dotarem® during pregnancy	Given that Dotarem® is not teratogenic in animals, an embryotoxic or teratogenic effect of Dotarem® in human is unlikely. No dedicated clinical trials have been performed on pregnant women. Data from about 150 post-marketing reports of exposure during pregnancy to date do not indicate a safety concern. Congenital anomaly/birth defect and adverse outcomes of pregnancies have been rarely observed following exposure to GBCA. A large number of pregnancies carried to term resulted in normal babies. However, there is no sufficient data available from exposed human pregnancies to adequately assess whether this is a potential risk in human. The risk is considered low, but cannot been ruled out. Therefore, GBCA-enhanced contrast imaging should be avoided if possible, but the benefits may outweigh the risk for certain conditions.
- Clinical significance of gadolinium retention in the brain	Several articles published in international scientific journals suggest that gadolinium accumulate in skin, bone and, in specific regions of the brain (globus pallidus and dentate nucleus) of patients with normal renal function receiving multiple administrations of GBCAs.

Missing information	What is known
- Clinical significance of Gadolinium accumulation in organs and tissues other than brain tissues	Nevertheless, it is not known what the effects of Gd deposition are. Clinical trials investigating gadolinium accumulation in bone, brain and other organs/tissues and their clinical consequences are currently underway.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a 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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
BONE study (DGD-44-056): Exploratory evaluation of the potential for long-term retention of Gadolinium in the bones of patients who have received Gadolinium based Contrast Agents according to their medical history	-To evaluate the potential for long-term retention of Gd in bones in patients having received gadolinium contrast -To prospectively explore the potential for long-term retention of gadolinium in bone in patients having received a single dose of GBCA or multiple doses of the same GBCA, with severe or moderate renal impairment or normal renal function at the time of GBCA injection.	Gadolinium accumulation in organs/tissues, including long-term effects	Started	2016
Kobe Joint Study (Prospective joint study in Japan)	-To measure Gd of resected bone by ICP-MS method with the purpose to determine the Gadolinium deposit in	Gadolinium accumulation in organs/tissues, including long-term effects	Started	2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	human bone tissue after administration of Gadolinium contrast agent either macrocyclic (Gd-DOTA) or linear (Gd-DTPA-BMA) chelates at a standard clinical dose and to evaluate the potential correlation with renal function (eGFR).			
NSsaFe study (DGD-55-003): Observational Study on the incidence of NSF in renal impaired patients following Dotarem® administration with a 2 year follow-up	-Primary: To estimate the incidence of NSF in patients with moderate to severe renal impairment after administration of Dotarem -Secondary: To collect a large number of data concerning the general safety profile of DOTAREM®, MRI indication, and conditions of use/administration of the product in this specific population of patients.	NSF	Started	2018
Pr Roberts, Charleston, USA. Potential of retention of gadolinium in brain.	Explore the correlation between the number of previous administrations of a GBCA and high signal intensity (SI) in brain in patients who have received Magnevist (n=15) or Dotarem (n=15).	Retention of gadolinium in brain	Started	First results, 2016
Pr Roberts, Charleston, USA. Potential of retention of	To determine the gadolinium concentration in skull bone tissue in paediatric patients requiring craniotomy and	Retention of gadolinium in organs/tissues other than brain	Started	First results, 2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
gadolinium in organs/tissues other than brain.	having received Magnevist® or Dotarem®.			
Pr A. Towbin, Cincinnati, USA. Potential of retention of gadolinium in brain and organs/tissues other than brain.	To determine if there is a relationship between the pre-contrast T1-weighted signal intensity and lifetime total gadolinium dose for different GBCAs. To determine the patterns of potential deposition (inferred by increased T1-weighted signal) within the brain and body (myocardial septum, liver, spleen, pancreas, kidney, skeletal muscle, bone) for different GBCAs.	Retention of gadolinium in brain and organs/tissues	Started	First results, 2016
Pr Houston, Dundee, United Kingdom	Detection of hypersignals in brain of patients with various CNS diseases having received several GBCAs including Dotarem®.	Retention of gadolinium in brain	Started	End 2016
Pr Cotton, Lyon, France Detection of hypersignals in patients with CNS disease.	Detection of hypersignals in brain of patients with multiple sclerosis having received several GBCAs including Dotarem®.	Retention of gadolinium in brain	Planned	First results mid 2017
Non-clinical study: Analysis of Gd speciation in the brain, especially areas associated with T1 hypersignal.	Various bioanalytical techniques will be used to determine the nature and concentrations of Gd deposits following repeated administrations of GBCAs to rats.	Retention of gadolinium in brain	planned	
Non-clinical study:	Investigate the long-term Gd deposition with	Retention of gadolinium in	planned	

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Investigate the long-term Gd deposition kinetics in the cerebellum of rats.	repeated administrations of GBCAs belonging to all molecular categories. 5-month follow-up (MRI at 4.7T and total Gd concentration in relevant structures of the brain).	brain		
Non-clinical study: Nature of Gd deposits in various sub-structures of the cerebellum.	To investigate and describe the nature of Gd deposits in various sub-structures of the cerebellum. Technique: Transmission electron microscopy and spectroscopy characterization of Gd and other metals in the cerebellum of rats chronically treated with all categories of GBCAs; in-depth histopathological study.	Retention of gadolinium in brain	Planned	
Investigate the potential neurotoxicity of accumulated GBCAs.	To investigate neuro-behaviour in rats chronically-treated with various GBCAs (at various time-points).	Clinical significance of gadolinium retention in the brain.	Planned	
Investigate the potential neurotoxicity of accumulated GBCAs.	Investigate the potential neurotoxicity of accumulated GBCAs with Microdialysis investigations	Clinical significance of gadolinium retention in the brain.	Planned	

Studies which are a condition of the marketing authorisation

The BONE study (DGD-44-056) is a condition of the marketing authorisation.

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
1	2007		Creation
2	29 July 2009	NSF added as potential risk.	Submission as requested per EU referral regarding NSF and populations at risk for this disease (referral under Article 31 of Directive 2001/83/EC as amended).
3	12 November 2009	NSF changed from potential to identified risk, addition of accumulation of gadolinium in tissues as important missing information	Revision as requested per above EU referral.
4	23 February 2011		General update, including individual case safety reports of NSF study synopsis regarding accumulation of gadolinium in tissues.
5	29 August 2011		General update, including individual case safety reports of NSF.
6	5 September 2012		General update, including individual case safety reports of NSF, inclusion of all safety concerns and new RMP format.
7	04 January 2013	Deletion of anaphylaxis as safety concern.	Update, including change of safety specification.
8	15 January 2014	Addition of convulsions as important potential risk. Change of teratogenicity safety concern from important potential risk to important missing information	Update, including change of safety specification.
9	14 February 2014	Change in categorization of convulsions as important identified risk instead of important potential risk. Change in categorization of teratogenicity as important potential risk instead of important missing information.	Update, including change of safety specification.
10.0	09 April 2015	Addition of anaphylaxis as important identified risk. Inclusion of use of Dotarem® during pregnancy as missing information to replace Teratogenicity as important potential risk. Extension of missing information gadolinium accumulation in bone, including long-term effects to gadolinium accumulation in organs/tissues, including long-term effects.	Update as part of worksharing variation with the aim to come to the approval in all EU countries of one single updated RMP for Dotarem® and its generic version Gadoteric acid Guerbet that complies with the guidance in GVP V.
11.0	14 October 2015		Update in respect to requests from RMS according the assessment report on RMP v10.0.
12.0	23/05/2016	This last version (12) was requested during the final PSUR assessment	Update of the appropriate sections as well as the

Version	Date	Safety Concerns	Comment
		report (procedure number PSUSA/00001506/201504) where it was stated that the MAH had to address the following issues in the next version of the RMP: • Addition of the following important potential risks: - Accumulation and retention of gadolinium in the brain - Gadolinium accumulation in organs and tissues other than brain tissues • Addition of the following missing information: - Clinical significance of gadolinium retention in the brain - Clinical significance of Gadolinium accumulation in organs and tissues other than brain tissues,	pharmacovigilance plan and risk minimization.
13.0	XX October 2016	As requested by the assessment report of the RMP, procedure NL/H/xxxx/WS/176: Revision of the date of the submission of final study report of the Bone study Addition of the Secure study (deleted in version 12 of RMP) since the assessment report was not provided to Guerbet. Presentation of the study of Pr. Roberts in 2 parts based on the explored organs: brain or other tissues/organs.	

Version	Date	Safety Concerns	Comment
		Correction of the category (not 3) of the clinical and non-clinical studies to get insight in the gadolinium accumulation in the brain and other tissues. Risk minimisation measures : one table per new risk (accumulation in brain and tissues) and missing information (clinical significance of gadolinium accumulation in brain and tissues) instead of a single and global one is now presented.	