HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 December 2013

DOTAREM, solution for injection

Vial of 5 ml, (CIP: 34009 358 954 2 4)
Vial of 10 ml, (CIP: 34009 331 713 4 6)
Vial of 15 ml, (CIP: 34009 331 714 0 7)
Vial of 20 ml, (CIP: 34009 331 715 7 5)

DOTAREM, solution for injection, prefilled syringe

Prefilled syringe of 10 ml (CIP: 34009 358 953 6 3)
Prefilled syringe of 15 ml (CIP: 34009 338 403 0 3)
Prefilled syringe of 20 ml (CIP: 34009 338 404 7 1)

Applicant: Guerbet

INN	Gadoteric acid (in the form of gadolinium oxide)
ATC code (2013)	V08CA02 (Paramagnetic contrast media)
Reason for the review	**Renewal of inclusion** **Reassessment of the improvement in actual benefit at the applicant's request**
List concerned	**National Health Insurance** (French Social Security Code L.162-17), except for the 10 ml prefilled syringe presentation **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"Magnetic resonance imaging for:** **- cerebral and spinal diseases;** **- diseases of the vertebral column;** **- other whole-body pathologies (including angiography)."**

Actual Benefit	**The actual benefit of DOTAREM remains substantial.**
Improvement in Actual Benefit	**DOTAREM offers a minor improvement in actual benefit (level IV) in terms of safety over gadolinium-based contrast media presenting a high (OMNISCAN, MAGNEVIST) or moderate (MULTIHANCE) risk of nephrogenic systemic fibrosis according to the European Medicines Agency classification.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Dates (national procedures): - 8 March 1989: vials of 10, 15 and 20 ml - 13 February 1995: prefilled syringe - 25 February 2002: vial of 5 ml
Prescribing and dispensing conditions	List I

ATC Classification	2013	
	V	Various
	V08	Contrast media
	V08C	Magnetic resonance imaging contrast media
	V08CA	Paramagnetic contrast media
	V08CA02	Gadoteric acid

02 BACKGROUND

DOTAREM is a gadolinium (Gd) chelate used, on account of its paramagnetic properties, as a diagnostic contrast medium in magnetic resonance imaging (MRI). In France there are currently six gadolinium chelates on the market, which differ in the nature of the ligand used, in their structure (linear or macrocyclic), and in their charge (ionic or nonionic).

Since 2006, international pharmacovigilance data have revealed an association between the occurrence of a systemic pathology, nephrogenic systemic fibrosis (NSF), and exposure to gadolinium chelates. NSF is a rare (400 to 700 identified cases to date worldwide according to sources[1,2]) late (median time to onset of five weeks after exposure) and potentially fatal complication of gadolinium-based contrast media. It affects subjects with renal impairment and is characterised by cutaneous fibrosis that can spread to the muscles and other organs, such as the lungs, liver and heart.

In 2009, the European Medicines Agency (EMEA) carried out an evaluation of the risk of developing NSF for each gadolinium chelate and issued guidelines and a classification of proprietary medicinal products into three risk categories:[3,4]

- high risk: OMNISCAN, MAGNEVIST;
- moderate risk: MULTIHANCE;
- low risk: GADOVIST, PROHANCE, DOTAREM.

For all contrast media containing gadolinium salts, the EMA:

- warns of a risk of NSF in the elderly owing to reduced renal function;

[1] International Nephrogenic Systemic Fibrosis Registry. The International Center for Nephrogenic Systemic Fibrosis Research (ICNSFR); Yale University. http://www.icnfdr.org/

[2] Pirovano G, Munley J, Schultz, Parker J, Kirchin MA, Quince K, Spinazzi A. Nephrogenic systemic fibrosis: a review of published cases and results from three prospective observational studies. European Congress of Radiology. 2012;3:n.B-0699.

[3] European Medicines Agency guidelines on minimisation of the risk of nephrogenic systemic fibrosis associated with administration of contrast media containing gadolinium salts - Bulletin, 02/12/2009.

[4] EMEA. Assessment report for gadolinium-containing contrast agents. Procedure No. EMEA/H/A-31/1097. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500099538.pdf

- stresses the lack of data on the efficacy of using haemodialysis as NSF prophylaxis and for treating NSF in patients not on haemodialysis;
- emphasises the need to record the name and administered dose of gadolinium-based contrast medium in the patient's records.

The products presenting the highest risk of developing NSF (OMNISCAN, MAGNEVIST) are contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min), patients awaiting a liver transplant or who have recently received one, and in neonates.

Since 2010, the FDA has also taken the view, based on pharmacovigilance data, that some gadolinium chelates (OMNISCAN, MAGNEVIST and OPTIMARK, which is not on the market in France) present a higher risk of NSF[5] and has contraindicated their use in patients with acute renal failure or a glomerular filtration rate of less than 30 ml/min/1.73 m^2. In parallel with this, the American College of Radiology (ACR) has issued guidelines and a classification of proprietary medicinal products on the market in the United States according to the risk of occurrence of NSF.[6]

Table 1: Classification of gadolinium-based contrast media according to risk of occurrence of nephrogenic systemic fibrosis

Risk (EMA)	ACR group	Structure	Charge	Gadolinium chelate	Proprietary medicinal product
High	I	Linear	Nonionic	Gadodiamide (Gd-DTPA-BMA)	Omniscan
				Gadoversetamide (Gd-DTPA-BMEA)	OptiMARK*
			Ionic	Gadopentetate dimeglumine (Gd-DTPA)	Magnevist, Magnegita
Moderate	II	Linear	Ionic	Gadobenate dimeglumine (Gd-BOPTA)	MultiHance
	III			Gadoxetic acid disodium (Gd-EOB-DTPA)	Primovist*, Eovist*
				Gadofosveset trisodium	Vasovist*, Ablavar*
Low	II	Macro-cyclic	Nonionic	Gadobutrol (Gd-DO3A-butriol)	Gadovist
				Gadoteridol (Gd-HP-DO3A)	ProHance
			Ionic	Gadoterate meglumine (Gd-DOTA)	Dotarem

I: Products associated with the highest number of cases of NSF
II: Products associated with a low number of "pure" cases of NSF, i.e. cases where only one gadolinium-based contrast medium may be involved.
III: Products recently launched onto the market.
*: Products not on the market in France

These classifications were established on the basis of physiochemical properties, animal studies and pharmacovigilance data for different gadolinium chelates.

It is against this background that the applicant is seeking a review of the proprietary medicinal products DOTAREM for reinclusion on the list of medicines refundable by National Health Insurance for a 5-year period starting on 26 June 2007 (Official Gazette of 5 May 2009) and reassessment of the improvement in actual benefit.

[5] FDA. Drug Safety Communication: New warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. Sept 2013. http://www.fda.gov/Drugs/DrugSafety/ucm223966.htm
[6] ACR. ACR Manual on contrast media. Version 9. 2013. http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Contrast%20Manual/2013_Contrast_Media.pdf

03 THERAPEUTIC INDICATIONS

“Magnetic resonance imaging for:
- cerebral and spinal diseases;
- diseases of the vertebral column;
- other whole-body pathologies (including angiography).”

04 DOSAGE

“The recommended dose is 0.1 mmol/kg, i.e. 0.2 ml/kg, in adults, children and infants. […]”

05 THERAPEUTIC NEED

MRI is a non-invasive medical imaging technique that allows anatomical images to be obtained in two or three dimensions. In particular, anatomical MRI allows the identification of tumours or malformations through visualisation of the anatomical structure of an organ. MRI also allows the performance of functional imaging in order to study the function or activity of an organ. It may be carried out with or without injection of contrast medium and is a useful tool in diagnostics, in clinical decision-making and in therapeutic follow-up.

Products based on a gadolinium chelate are the most commonly used contrast agents when it is necessary for MRI to be carried out with injection of a contrast medium. These are diagnostic products, the use of which allows improved visualisation of structural or functional abnormalities.

06 CLINICALLY RELEVANT COMPARATORS

There are other gadolinium-based contrast media available that have similar indications. All these products are refundable by National Health Insurance and approved for hospital use.

Proprietary medicinal product (INN)	Manufacturer	Indication	Date of Opinion	AB	IAB (wording)
GADOVIST (Gadobutrol)	Bayer Santé	- MRI of the cranial and cerebral and spinal regions - MRI of the liver and kidneys - Angiography by MR	29/11/06	Substantial	V (versus other products of the class)
MAGNEGITA (Gadopentetic acid)	Insight Agents GmbH	MRI for: - cerebral and spinal diseases - diseases of the vertebral column - whole-body pathologies	Not evaluated (generic of MAGNEVIST)		
MAGNEVIST (Gadopentetic acid)	Bayer Santé	MRI for: - cerebral and spinal diseases - diseases of the vertebral column - whole-body pathologies	07/04/04	Substantial	V (versus standard treatment)
MULTIHANCE (Gadobenate dimeglumine)	Bracco Imaging France	- MRI of the liver - MRI of the central nervous system - Angiography by MR	05/09/01	Substantial	V (versus comparison medicinal products)
OMNISCAN (Gadodiamide)	GE Healthcare	MRI for: - cerebral and spinal diseases - diseases of the vertebral column - whole-body pathologies	02/04/03	Substantial	V
PROHANCE (Gadoteridol)	Bracco Imaging France	MRI for: - cerebral and spinal diseases - diseases of the vertebral column - whole-body pathologies	04/12/96	Substantial	V (versus other paramagnetic contrast media)

◗ Conclusion
The comparators listed are all clinically relevant.

07 ANALYSIS OF THE NEW DATA AVAILABLE

07.1 Efficacy

The applicant has submitted a literature review on the efficacy of DOTAREM covering 14 publications:

- one comparative study versus imaging without injection of contrast media;[7]
- seven comparative studies versus other gadolinium chelates;[8,9,10,11,12,13,14]

[7] Shah DJ, Lim TH. Evaluation of meglumine gadoterate-enhanced MR angiography (MRA) compared with time-of-flight MRA in the diagnosis of clinically significant non-coronary arterial disease: a pooled analysis of data from two clinical trials. Br J Radiol 2012; 85: 596-605
[8] Rasmus M, Bremerich J, Egelhof T, Huegli RW, Bongartz GM, Bilecen D. Total-body contrast- enhanced MRA on a short wide-bore 1.5-T system: intra-individual comparison of Gd-BOPTA and Gd- DOTA. Eur Radiol 2008; 18: 2265-73
[9] Szucs-Farkas Z, Froehlich JM, Ulrich M, Wuersten HU, Guignard D, Wyss S, Braunschweig M. 1.0- M gadobutrol versus 0.5-M gadoterate for peripheral magnetic resonance angiography: a prospective randomized controlled clinical trial. JMRI 2008; 27: 1399-1405

- three comparative studies versus other diagnostic methods not including medical imaging;[15,16,17]
- three open observational studies.[18,19,20]

No multicentre comparative study versus other gadolinium chelates carried out in the indications of the Marketing Authorisation in more than 30 patients and including an intention-to-treat analysis was submitted.

◗ These data are unlikely to alter the conclusions of the Transparency Committee's previous Opinion.

07.2 Adverse effects

7.2.1 General safety

Data from clinical studies

Nine of the studies relating to efficacy submitted by the applicant mention the observed adverse effects. These studies confirm the safety profile described in the SPC of DOTAREM, the majority of adverse effects being nausea, vomiting, pruritus and urticaria.

In addition, the applicant has submitted the results of two observational studies on tolerability immediately after injection of a gadolinium-based contrast medium:

- one prospective study that examined the development of adverse effects;[21]
- one retrospective study that examined the development of hypersensitivity reactions.[22]

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[10] Pennekamp W, Roggenland D, Hering S, Lemburg S, Peters S, Sterl S, et al. lntra-individual, randomised comparison of the MRI contrast agents gadobutrol and gadoterate in imaging the distal lower limb of patients with known or suspected osteomyelitis, evaluated in an off-site blinded read. Eur Radiol 2011; 21: 1058-67

[11] Anzalone N, Scarabino T, Venturi C, Cristaudo C, Tartare A, Scotti G, et al. Cerebral neoplastic enhancing lesions: multicenter, randomized, crossover intraindividual comparison between gadobutrol (1.0 M) and gadoterate meglumine (0.5 M) at 0.1 mmol Gd/kg body weight in a clinical setting. Eur J Radiol 2013;82:139-45.

[12] Wagner M, Schilling R, Doeblin P, Huppertz A, Luhur R, Schwenke C, et al. Macrocyclic contrast agents for magnetic resonance imaging of chronic myocardial infarction: intraindividual comparison of gadobutrol and gadoterate meglumine. Eur J Radiol (2012), doi 10.1007/s00330-012-2563-6

[13] Haneder S, Attenberger Ul, Schoenberg SO, Loewe C, Arnaiz J, Michaely HJ. Comparison of 0.5 M gadoterate and 1.0 M gadobutrol in peripheral MRA: a prospective, single-center, randomized, crossover, double-blind study. J Magn Reson lmaging.2012; 36: 1213-1221

[14] Papini GDE, Tritella S, Secchi F, Aliprandi A, Di Leo G, Sardanelli F. Myocardial delayed enhancement using a single dose (0.1 mmol/kg) of gadobenate dimeglumine: contrast resolution versus intraventricular blood and viable myocardium. Radiol Med 2010; 115 (5): 693-701

[15] Lin C, Luciani A, Belhadj K, Deux JF, Kuhnowski F, Maatouk M, Beaussart P, Cuenod CA, Haioun C, Rahmouni A. Multiple myeloma treatment response assessment with whole-body dynamic contrast-enhanced MR imaging. Radiology 2010; 254: 521-531

[16] Bali MA, Metens T, Denolin V, Delhaye M, Demetter P, Closset J, Matas C. Tumoral and nontumoral pancreas: Correlation between quantitative dynamic contrast-enhanced MR imaging and histopathologic parameters. Radiology 2011; 261: 456-466

[17] Veltman J, Stoutjesdijk M, Mann R, Huisman HJ, Barentsz JO, Blickman JG, Boetes C. Contrast- enhanced magnetic resonance of the breast: the value of pharmacokinetic parameters derived from fast dynamic imaging during initial enhancement in classifying lesions. Eur. Radiol. 2008; 18: 1123- 1133

[18] Emond S, Brunelle F, Khalfi F, Dubourdieu C. Gd-DOTA administration at MRI in children younger than 18 months of age: immediate adverse reactions. Pediatr Radiol 2011; 41: 1401-6

[19] Ishiguchi T, Takahashi S. Safety of gadoterate meglumine (Gd-DOTA) as a contrast agent for magnetic resonance imaging: results of a post-marketing surveillance study in Japan. Drug RD 2010; 10: 133-145

[20] Maurer M, Heine 0, Wolf M, Durmus T, Wagner M, Hamm B. Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: results in more than 84,000 patients. European Journal of Radiology 2012; 81: 885-890

[21] Bruder O, Schneider S, Nothnagel D, Pilz G, Lombardi M, Sina A, et al. Acute adverse reactions to gadolinium-based contrast agents in CMR. Multicenter experience with 17,767 patients from the euroCMR registry. JACC: Cardiovasc lmaging 2011; 4 (11): 1171-6

[22] Jung JW, Kang HR, Kim MH, Lee W, Min KU, Han MH, Cho SH. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. Radiology 2012; 264 (2): 414-22

The incidence of reactions observed with DOTAREM was similar to that of other gadolinium chelates (immediate adverse effects in 3 out of 1208 cases, i.e. 0.25%, and immediate hypersensitivity reactions in 31 out of 38,580 cases, i.e. 0.080%).

Pharmacovigilance data

The applicant has submitted the five periodic safety update reports (PSURs) covering the period from 1 October 2007 to 30 September 2012. On the assumption that one dose corresponds to one patient treated, exposure to gadoteric acid during this period is estimated at 20,689,879 patients worldwide. During this period, 1360 cases of adverse effects were reported, 1073 (78.9%) of these by healthcare professionals. A total of 480 serious cases (35.3%) were reported, of which 18 were fatal. The causes of death were NSF (7 "mixed" cases, in which the patient had received more than one different contrast medium before developing this condition), an anaphylactic reaction or cardiorespiratory arrest (9 cases), cardiac decompensation (1 case) and haemorrhage (1 case).

Changes to the SPC

Since the previous Committee Opinion of 21 January 2009, some changes have been made to the SPC of DOTAREM for the purposes of European harmonisation:

- Section 4.3 Contraindications: "*history of hypersensitivity to gadoteric acid, to meglumine or to any medicinal products containing gadolinium*".
- Section 4.4 Special warnings and precautions for use: "*gadoteric acid must not be administered by subarachnoid (or epidural) injections*"
    - Subsection 4.4.1 Special warnings: "*There is always a risk of hypersensitivity regardless of the dose injected*"; "*The injection of gadoteric acid may aggravate symptoms of an existing asthma. In patients with asthma unbalanced by the treatment, the decision to use gadoteric acid must be made after careful evaluation of the risk/benefit ratio*"; "*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*";
    - Subsection 4.4.2 Precautions for use: "*Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume*"; "*In patients with a history of seizures there is an increased risk of further episodes*".
- Section 4.5 Interaction with other medicinal products and other forms of interaction: "*No interactions with other medicinal products have been observed. Formal drug interaction studies have not been carried out*".
- Section 4.8 Undesirable effects:
    - Change to or addition of the frequencies of certain adverse effects, including headache and paresthesia (very common > 1/10) and nausea, vomiting and skin reactions (common > 1/100 to < 1/10);
    - Addition in "*Investigations: Very rare: decreased oxygen saturation*".

7.2.2 Specific safety

Nephrogenic systemic fibrosis is a sclerodermiform disorder described for the first time in 1997 in dialysis patients. It is manifested in the form of skin lesions starting most often in the legs before spreading to the arms and trunk, but not the face and neck. The lesions appear in the form of indurated brownish plaques or papules often in association with an orange skin coloration. These skin lesions can cause difficulty in extending joints, resulting in impaired mobility. In addition, systemic lesions involving organs such as the heart and lungs may be observed. The prognosis in NSF depends on the extent and severity of the fibrosis. A progressive deterioration in clinical state is generally observed, leading to death in 20 to 30% of cases. There is currently no treatment of proven efficacy in this pathology.

The causal factor in NSF is exposure to gadolinium-based contrast media. The median time to onset of the first symptoms is five weeks (most often between two and ten weeks) after exposure. There are two types of NSF: “pure” (or “non-mixed”) cases, in which the patient had received only a single type of contrast medium, and “mixed” cases, in which the patient had received more than one gadolinium-based contrast medium (identical or otherwise) prior to developing the pathology. Numerous risk factors also seem to contribute to the development of this complication. For example, all the patients who developed NSF had renal impairment (GFR < 30 ml/min). The dose, the frequency and the chemical structure of the gadolinium chelate used also appear to influence the risk of NSF, as the majority of cases have been observed after more than one high-dose injection of certain gadolinium chelates. Other factors, such as use of high doses of erythropoietin, the presence of metabolic acidosis, increased calcium phosphate product or the presence of a chronic inflammatory syndrome remain controversial.

The physiopathology of NSF has not been clearly established. The most popular current hypothesis involves dissociation of the gadolinium chelate by a transmetallation process, i.e. competition between endogenous ions (zinc, copper, iron, calcium, etc.) and gadolinium ions for the chelation sites. This process would allow the release into the circulation of gadolinium in the uncomplexed state. The gadolinium would then undergo deposition in the tissues after binding to an anion such as phosphate, resulting in the activation of circulating fibrocytes. The transmetallation would be favoured by higher levels of exposure (increased dose and/or frequency, reduced elimination, particularly in patients with renal impairment, etc.) and by the poorer stability of some gadolinium chelates.

The incidence of this complication is estimated at not more than 3.5% in highest-risk situations (injection of gadodiamide in dialysis patients), but seems much lower in kidney transplant patients or patients with a GFR < 30 ml/min and is almost zero when the GFR is greater than 30 ml/min.[5,23,24]

Physiochemical study data

The different gadolinium chelates differ in their structure (linear or macrocyclic) and charge (ionic or nonionic). These properties determine the physicochemical stability of the molecule:

- linear complexes have lower thermodynamic stability than macrocyclic complexes and consequently dissociate more easily;
- ionic complexes have lower kinetic stability than nonionic complexes and consequently dissociate more rapidly.

[23] Mailliez S, Jauréguy J, Renou M et al. Nephrogenic systemic fibrosis in chronic renal impairment. In: Actualités néphrologiques 2008.
http://www.soc-nephrologie.org/PDF/enephro/publications/actualites/2008/2008_16.pdf

[24] Amel S, Clément O, Frances C, et al. French prospective study on nephrogenic systemic fibrosis in hemodialysis patients after contrast media administration: results of the Pro-FINEST study. J Pharm Clin 2012; 31(3): 149-58

These data point to the poorer stability of linear gadolinium complexes (greater dissociation) compared with macrocyclic complexes. In addition, nonionic character seems to be an unfavourable characteristic when there is significant (faster) dissociation.

Clinical study data
The applicant has submitted the results of three observational studies that sought to determine the incidence of NSF in patients with renal impairment after MRI with or without injection of contrast medium.[24,25,26] One of these studies resulted in the retrospective identification of six cases of NSF in 367 patients with end-stage renal failure who had been treated with a gadolinium chelate (1.6%). Of the 325 MRI investigations for which the contrast medium was known, 153 were carried out with OMNISCAN (47.1%), 64 with MAGNEVIST (19.7%), 56 with DOTAREM (17.2%), 17 with GADOVIST (5.2%), 15 with PROHANCE (4.6%), 12 with MULTIHANCE (3.7%) and 8 with PRIMOVIST (2.5%). The contrast media thought to be involved in the six observed cases of NSF were: OMNISCAN (two "pure" and four "complex" cases), MAGNEVIST (two "complex" cases) and DOTAREM (two "complex" cases).

Pharmacovigilance data
Exposure to gadoteric acid since first market launch in 1989 is estimated at some 37 million patients worldwide. During this period there were 15 reported "mixed" cases of NSF in which DOTAREM may have been involved, including five in which the clinical and histological diagnosis is well established. No change to the SPC concerning the risk of NSF has been made since the previous Committee Opinion of 21 January 2009.

Risk management plan
Since 2009, all gadolinium-based contrast media have come under a European risk management plan focussing on NSF. A prospective study seeking to identify any suspicion of NSF in over 40,000 patients with renal impairment is currently underway as part of this plan.

◗ The risk of NSF led the European and US medicines agencies to establish guidelines[4,5] on the use of gadolinium-based contrast media (Table 3) and a classification of these products according to their level of risk (Table 2). The Japanese health authorities,[27] the European Society of Urogenital Radiology[28] (ESUR) and the American College of Radiology[6] have issued guidelines similar to those of the EMA and the FDA.

The incidence of NSF appears to have decreased since the publication of these guidelines.[29]

[25] Janus N, Launay-Vacher V, Karie S, et al. Prevalence of nephrogenic systemic fibrosis in renal insufficiency patients: results of the FINEST study. European Journal of Radiology 2010; 73: 357-359
[26] Heinz-Peer G, Neruda A, Walsch inger B, et al. Prevalence of NSF following intravenous gadolinium-contrast media administration in dialysis patients with end-stage renal disease. Eur J Radiol 2010; 76: 129-134
[27] PMDA. Pharmaceuticals and Medical Devices Safety Information. No. 285 November 2011
[28] Thomsen HS, Morcos SK, Almén T, Bellin MF, Bertolotto M, Bongartz G, Clement O, Leander P, Heinz-Peer G, Reimer P, Stacul F, van der Molen A, Webb JA; ESUR Contrast Medium Safety Committee. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol. 2013 Feb;23(2):307-18. doi: 10.1007/s00330-012-2597-9. Epub 2012 Aug 4. Review.
[29] Wang Y, Alkasab TK, Narin O, et al. Incidence of nephrogenic systemic fibrosis after adoption of restrictive gadolinium-based contrast agent guidelines. Radiology. 2011 Jul;260(1):105-11. doi: 10.1148/radiol.11102340. Epub 2011 May 17.

Table 2: Classifications of gadolinium-based contrast media according to the risk of occurrence of nephrogenic systemic fibrosis and principal factors

Risk (EMA)	ACR group	Structure	Charge	Thermo-dynamic stability constant (at pH 7.4)	Dissociation half-life (at pH 1.0 and 25°C)	Gadolinium chelate	Proprietary medicinal products	France	Europe		USA		
								Year MA was granted	Units sold up to 2009 [millions]	Number of pure cases of NSF to end of 2008	Year MA was granted	Market share in 2008 [%]	Number of pure cases of NSF to end of 2008
High	I	Linear	Nonionic	14.9	< 5 s	Gadodiamide	Omniscan	1994	47	438	1993	20	382
				15.0	< 5 s	Gadoversetamide	OptiMARK*	-	0.8	7	1999	NR	35
			Ionic	17.7	< 5 s	Gadopentetate dimeglumine	Magnevist, Magnegita	1988	95	135	1988	50	195
Moderate	II	Linear	Ionic	18.4	< 5 s	Gadobenate dimeglumine	MultiHance	1998	6	0	2004	NR	1
	III			18.7	< 5 s	Gadoxetic acid disodium	Primovist*, Eovist*	-	0.15	0	2008	NR	0
				18.9	< 5 s	Gadofosveset trisodium	Vasovist*, Ablavar*	-	0.05	0	2008	NR	0
Low	II	Macro-cyclic	Nonionic	14.7	43 h	Gadobutrol	Gadovist	2000	2.6	0	2011	NR	N/A
				17.1	3,9 h	Gadoteridol	ProHance	1994	12.3	1	1992	NR	0
			Ionic	19.3	338 h	Gadoterate meglumine	Dotarem	1989	22.4	0	2013	NR	N/A

I: Products associated with the highest number of cases of NSF
II: Products associated with a low number of pure cases of NSF
III: Products recently launched onto the market.

NR: Not recorded
N/A: Not applicable
*: Products not on the market in France

Table 3: Guidelines on the risk of occurrence of nephrogenic systemic fibrosis

Product	EMA	FDA
Omniscan, OptiMARK*, Magnevist, Magnegita	- Contraindication in severe RI and after liver transplantation. - Precaution for use in moderate RI, depending on risk/benefit ratio. Use minimum diagnostic dose, 7 days between two MRI	- Contraindication in acute or severe RI.
MultiHance, Primovist*, Vasovist*	- To be avoided in severe RI and after liver transplantation. Use minimum diagnostic dose, 7 days between two MRI	- To be avoided in patients in whom the elimination of drug substances is impaired (known or suspected)
Dotarem, Gadovist, ProHance	- Precaution in severe RI and after liver transplantation. Use minimum diagnostic dose, 7 days between two MRI	

07.3 Usage data

The unit sales data for DOTAREM of all sectors taken together (pharmacies and hospitals) between January 2012 and December 2012 (GERS data) are shown below.

DOTAREM presentations	GERS sales data (boxes)
Vial of 5 ml	10,426
Vial of 10 ml	79,599
Vial of 15 ml	279,366
Vial of 20 ml	424,271
Syringe of 10 ml	26,585
Syringe of 15 ml	1,700,949
Syringe of 20 ml	1,245,216

DOTAREM is the most commonly used paramagnetic contrast medium in France (approx. 60% of sales of gadolinium-based contrast media according to the GERS data for 2012).

07.4 Diagnostic strategy

Paramagnetic contrast media generally allow better visualisation of anatomical or vascular structures by improving the quality of images obtained by magnetic resonance. Examinations using these products are carried out according to the “Guide to the proper use of medical imaging investigations”[30] updated in 2013 by the French Radiology Society, which sets out the role of different investigations according to pathology.

Since the last assessment by the Committee, the role of DOTAREM in the diagnostic strategy has remained unchanged. Like other gadolinium-based contrast media, it remains a first-line product when a MRI examination using contrast medium is necessary.

[30] Guide to the proper use of medical imaging investigations SFR 2013- http://gbu.radiologie.fr/

08 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

08.1 Actual benefit

- The degree of seriousness of the condition is not known until the MRI examination has been performed.
- DOTAREM is a product intended for diagnostic use. It can be used to improve the contrast in MRI in order to boost the detection of structural or functional abnormalities.
- The efficacy/adverse effects ratio in the indications of the Marketing Authorisation is high.
- Diagnostic alternatives are available.
- DOTAREM is intended for use in first-line diagnostic examinations.

- Public health benefit: In the absence of data on the diagnostic benefit of DOTAREM compared with the available alternatives, it is not possible to quantity its impact on the health of patients requiring diagnostic examinations by magnetic resonance imaging with use of contrast media.

  Given the availability of other contrast media for magnetic resonance imaging and of the therapeutic alternatives, DOTAREM is not expected to benefit public health.

Taking account of these points, the Committee considers that the actual benefit of DOTAREM remains substantial in the indications of the Marketing Authorisation.

08.2 Improvement in actual benefit (IAB)

Based on the available data, the Committee considers that DOTAREM offers a minor improvement in actual benefit (level IV) in terms of safety over gadolinium-based contrast media presenting a high (OMNISCAN, MAGNEVIST) or moderate (MULTIHANCE) risk of nephrogenic systemic fibrosis according to the European Medicines Agency classification.

08.3 Transparency Committee Recommendations

The Committee recommends continued inclusion of DOTAREM on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indications of the Marketing Authorisation.

- **Proposed reimbursement rate: 65%**
- **Packaging:** Appropriate for the prescription conditions.