CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204781Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMAOCLOGY NDA REVIEW

NDA:	204-781
Type/Category:	New NDA, Original-1 (Type 1- New Molecular Entity), 1S
Brand name:	Dotarem (Meglumine gadoterate) Injection
Proposed indication:	Dotarem is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonates to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
Route of Administration:	Intravenous Injection
Applicant:	Guerbet, LLC
Reviewing Division:	Division of Clinical Pharmacology 5 (DCP 5)
Medical Division:	Division of Medical Imaging Products (DMIP)
Submission Dates:	September 20, 2012, SDN 1 October 30, 2012 SDN 3 October 31, 2012, SDN 4 December 31, 2012, SDN 8 February 06, 2013, SDN to be determined
Primary Reviewer:	Christy S. John, Ph.D.
Secondary Reviewer:	Gene Williams, Ph.D.

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1. Executive Summary

Guerbet, LLC has submitted a New Drug Application for Dotarem (Meglumine gadoterate) Injection to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity in adults and pediatric patients (from birth onward). Dotarem was first approved in France in March 1989 and has been approved in more than 70 countries.

The proposed dose is 0.1 mmol/kg body weight to be administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second for adults and 1-2 mL/second for children. There was no dose finding study conducted by the applicant. The dose was selected based upon information from other gadolinium based contrast agents (GBCAs).

Four clinical pharmacology studies, all performed in healthy volunteers rather than patients receiving CNS imaging, have been conducted in support of this NDA. A descriptive pharmacokinetic (PK) and excretion study (DG 3-6) was performed in healthy males. A second PK study (DGD 3-48) was conducted to assess the effect of acute repeat dosing (0.1 mmol/kg followed by 0.2 mmol/kg). The PK were linear. A specific population PK Study (DGD 3-28) was conducted in subjects with renal impairment. The results, showed renal elimination decreases as renal impairment increases. The AUC was 9-fold higher in patients with severe renal impairment. The fourth clinical pharmacology study assessed QT_C. Gadoterate had no effect on QT_C.

Although a dramatic effect of renal impairment on concentrations was observed, we do not recommend dose adjustments for patients with renal impairment. Because imaging is conducted shortly after drug administration (i.e., before much clearance can occur), reducing dose to adjust AUC to that occurring in non-impaired subjects risks compromising imaging. Because of the safety profile of Dotarem, experience with other GBCAs, and the class labeling (black box warning) for the risk of the life-threatening adverse event NSF (nephrogenic systemic fibrosis) in patients with severe renal impairment, we do not recommend dose adjustment for renal impairment or a post-marketing commitment to further study if renally impaired patients can be successfully imaged at a reduced dose.

The applicant is seeking approval in pediatric subjects, including those under the age of two years. There is no pharmacokinetic data to establish an optimal dose for those under two. Further, there is very limited clinical data to assure safety in this age group. Since renal impairment dramatically changes excretion of drug, we are concerned that in children < 2 years, where renal maturation may be incomplete, safety may be compromised. We recommend a Post-Marketing Requirement (PMR) to obtain data in children under two years of age.

1.1. Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 5 has reviewed NDA 204-781. The application is acceptable from a clinical pharmacology standpoint, provided an agreement is reached in labeling.

1.2. Post-marketing Requirements and Commitments

PMC or PMR	Key drug development question	Rationale	Design summary
PMR	Is Dotarem reasonably likely to be efficacious and safe for patients under 2 years of age?	PK,imaging and safety data are necessary to inform dosing in children less than 2 yrs of age. If early concentrations (those occurring at the time of imaging) are significantly increased, the PK data will provide a rational basis for lowering the dose.	**Study population:** children less than 2 years of age undergoing CNS imaging, and healthy adult subjects to allow comparison of results (no adult data on the presence of non-parent gadolinium are available) **Study design:** unblinded, single dose, two arms: 1) children less than 2 years of age, and 2) adults if interim PK results (n=15) show potential that a lower dose could retain imaging success while decreasing exposure, a lower dose will be estimated and investigated in the remaining 25 patients **Sample size:** Children less than 2 years of age arm: n = 40; with 3 PK samples/child (randomized block sampling with 3 periods, one of which is close to the end of infusion) has been used in a previous PMR trial of a GBCA in children less than 2 years of age. Adult arm: n = 10; this should be sufficient to characterize non-parent gadolinium in adults **Dose:** 0.1 mmol/kg **Endpoints:** plasma PK and urinary excretion of total and free gadolinium; imaging endpoints for the children less than 2 years of age arm

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Dotarem is a Gadolinium-based contrast agent (GBCA) intended for use in MRI of the CNS. There are six similar agents currently approved in the United States.

The proposed dose is 0.1 mmol/kg body weight to be administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second for adults and 1-2 mL/second for children. There was no dose finding study conducted by the applicant. The clinical dose was based upon information from previously developed GBCAs.

Dotarem, like other gadolinium contrast agents, has a relatively short elimination half-life (1.32 ± 0.24 hours). Dotarem volume of distribution approximates extracellular space. (about 16 L in males). *In vitro* plasma protein binding was less than 4%. After a single intravenous injection of 0.1 mmol/kg to healthy subjects, 86.6±10.3 % of the Gd dose was recovered in urine over 48 h (Study DGD 3-6).

The applicant repeatedly states that Dotarem does not undergo metabolism and is excreted as a parent. There is no direct evidential data for such a claim. In all analytical methods for measurement of gadolinium, an ICP/OES method was used. The plasma or urine samples were processed using nitric acid and hydrogen peroxide and total gadolinium content was measured. An IR was sent to the applicant to provide evidence that the parent was excreted in urine. PK of the drug and its relevant metabolites were not reported for patients.

The effect of repeat dosing (i.e., administration of a second dose which might be performed in clinical practice if the scan following the initial dose was not performed or unsuccessful) was investigated Following administration of an initial dose of 0.1 mmol/kg and a subsequent dose (20 min after the initial dose) of 0.2 mmol/kg, pharmacokinetics were linear.

A PK study in non-dialyzed subjects with renal impairment was performed. As might be anticipated for a drug eliminated completely or nearly completely via the renal route, exposure was dramatically increased in impaired subjects. AUC in patients with severe renal impairment was 9-fold that of non-impaired subjects. Moderately impaired subjects had AUCs 5-fold those of non-impaired subjects. Because imaging is conducted shortly after drug administration (i.e., before much clearance can occur), reducing dose to adjust AUC to that occurring in non-impaired subjects risks compromising imaging. Because

1. gadoterate causes very limited adverse events,
2. other approved GBCAs, which also show dramatic increases in AUC in those with renal impairment, do not have recommendations for dose adjustment for renal impairment,
3. gadoterate has very high thermodynamic and kinetic stability: while *in vivo* stability was not assessed, the apparent likelihood of free Gd, which might be a safety risk, is less for gadoterate than the other GBCAs, and

4. Doatarem will receive class labeling (black box warning) for the risk of the life-threatening adverse event NSF (nephrogenic systemic fibrosis) in patients with severe renal impairment. The prescribing community (radiologists) are acutely aware of the risks of administering GBCAs to renal impairment patients. The use of GBCA in patients with renal impairment is almost non-existent due to legal liabilities (anecdotal communications from radiologists),

we do not recommend dose adjustment for renal impairment or a post-marketing commitment to further study if renally impaired patients can be successfully imaged at a reduced dose.

The applicant also conducted three pilot studies of Dotarem in pediatric patients. There were 38 children enrolled in the primary Phase 3 efficacy study, Study DGD-50. However, no PK data were collected in any of the studies. The applicant is seeking an indication for all pediatric patients (no lower age limit). The total clinical trails database includes only seven patients under two years of age. We recommend a post-marketing commitment to study patients under two years of age (see **1.2. Post-marketing Requirements and Commitments**).

2. Question Based Review

2.1. What *In Vitro* and *In Vivo* Clinical Pharmacology and Biopharmaceutics studies and Clinical Studies contributed PK and/or PD information to the application?

The applicant has conducted four studies that contributed PK or PD information to the application (**Table 1.**).

Table 1. PK and PD studies of Gd-DOTA conducted in support of NDA

DGD-3-06	Study of excretion of Dotarem in blood, urine and feces in healthy male volunteers	Phase I, single center, open label, nonrandomized
DGD-3-28	Study of the pharmacokinetics of Dotarem in patients with chronic renal failure	Phase I, single center, open-label, nonrandomized
DGD-44-039	Evaluation of the electrocardiographic safety in patients	Phase II b, single center, open-label, nonrandomized
DGD-3-48	PK study of Gd-DOTA after 0.1 mmiol/kg +0.2 mmol/kg IV injections in healthy male and female volunteers	Phase I, single center, open-label, nonrandomized

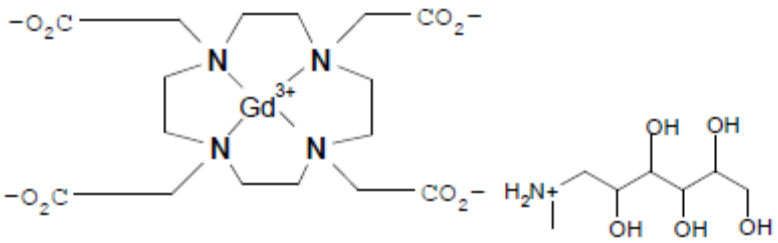
2.2. General Attributes of the Drug

2.2.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Dotarem (gadoterate meglumine) Injection is a paramagnetic macrocyclic contrast agent administered for magnetic resonance imaging. The chemical name for gadoterate is 1, 4, 7, 10 tetrazacyclododecane N, N', N'', N'''-tetraacetic acid gadolinium. It has a molecular weight of 753.9 g/mol and an empirical formula of $C_{23}H_{42}O_{13}N_5Gd$.

The structural formula of gadoterate meglumine is shown below.

Figure 1.



The drug product is a sterile, clear, colorless to yellow, aqueous solution for intravenous injection containing 376.9 mg/mL gadoterate meglumine (equivalent to 0.5 mmol/mL) and is available in vial and pre-filled syringe. The major physico-chemical properties of Dotarem are listed in **Table 2.**

Table 2. Physico-chemical properties of Dotarem.

Parameter	Value
Density @ 20°C	1.1753 g/cm^3
Viscosity @ 20°C	3.4 mPa.s
Viscosity @ 37°C	2.4 mPa.s
Osmolality	1350 mosm.kg^{-1}
pH	6.5 to 8.0

2.2.2. What are the proposed mechanism of action and therapeutic indications?

Section 12.1 of the package insert is reproduced.

> Gadoterate meglumine is a paramagnetic agent that develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment can enhance the relaxation rates of water protons in its vicinity, leading to an increase in signal intensity (brightness) of tissues.

2.2.3. What are the proposed dosages and routes of administration?

The proposed dose is 0.2 mL/kg (0.1 mmol/kg) body weight for both adults and children (no lower age limit) administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second for adults and 1-2 mL/second for children.

2.2.4. What drugs (substances, products) indicated for the same indication are approved in the US?

Currently, there are six extracellular contrast agents approved in USA for use in MRI of the CNS **(Table 3.**). Indications for use and efficacy are similar for these agents. All GBCAs are comprised of the same principle components: a gadolinium ion linked to a complexing agent (ligand). However, GBCAs differ in a number of properties, such as chemical structure (linear versus macrocyclic), thermodynamic stability, kinetic stability (i.e., time course of dissociation of gadolinium), ionicity, concentration, osmolality, viscosity, pharmacokinetics, and relaxivity (a measure of their ability to enhance tissue during MRI exams) these characteristics have implications for diagnostic performance safety.

Table 3. Gadolinium binding contrast agents (GBCAs), and their stability constants

Gadolinium-Chelate	Type	Thermodynamic Stability		Kinetic Stability (Dissociation Half-life) T1/2 at pH 1.0 at 25°C
		Log K_{therm} [1]	Log K_{cond} [2] at pH 7.4	
Dotarem®	Ionic macrocyclic	25.6	19.3	> 338 h
MultiHance®	Ionic linear	22.6	18.4	< 5 s
Magnevist®	Ionic linear	22.1	17.7	< 5 s
ProHance®	Non-ionic macrocyclic	23.8	17.1	3.9 h
Gadavist™	Non-ionic macrocyclic	21.8	14.7	43 h
Omniscan™	Non-ionic linear	16.9	14.9	< 5 s
Optimark™	Non-ionic linear	16.6	15.0	< 5 s

(1) Log K_{therm} = absolute thermodynamic stability constant
(2) Log K_{cond} = conditional thermodynamic stability constant depending on pH

2.3. General Clinical Pharmacology

2.3.1. What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

No dose finding study was conducted by the applicant. The applicant states, "Gadolinium contrast agents are usually used at a dose of 0.1 mmol/kg and this dose was already recognized in the literature as being the effective dose for gadolinium complexes and already being used for Magnevist, whose general pharmacokinetics and effects on MRI signals are identical to those of Dotarem. Therefore, dose of 0.1 mmol/kg for Dotarem was deliberately selected at the time of the very first preclinical and clinical trials. In most studies presented in this submission, Dotarem dose was 0.1 mmol/kg (i.e. 0.2 mL/kg)."

The applicant conducted two pivotal trials (DGD-44-50 in adults and pediatric patients and DGD-3-44 conducted in adults) to demonstrate the efficacy of Dotarem. MR images were acquired and compared, uncontrast (U) images were compared to images with contrast (while the uncontrast image was still present: uncontrast images + contrast = U+C). The primary endpoints were tumor visualization (border delineation, internal morphology, and contrast enhancement). The images were scored as 0 for un-evaluable, 1

for seen but not clearly and 2 for perfectly seen. The scores per reader per subject were summed for all three primary endpoints and compared as pre (U) to paired (U+C). All three readers scores were high for paired read (U+C) as compared to precontrast (C) reads (**Table 3.**), implying better lesion visualization with Dotarem.

Table 3. Primary Endpoint Results for Study 050: Patient Scores for Lesion Visualization, by Reader (mean, SD)

Readers	**Reader 1**		**Reader 2**		**Reader 3**	
Modality	Pre	Paired	Pre	Paired	Pre	Paired
N Patients*	224	230	224	230	222	235
Border Delineation Score						
Mean **SD**	1.06 (1.23)	3.30 (2.64)	1.62 (1.43)	4.49 (2.94)	1.43 (1.29)	2.54 (2.30)
Internal Morphology Score						
Mean **SD**	0.97 (1.05)	3.70 (2.63)	1.76 (1.24)	4.49 (2.93)	1.45 (1.13)	2.93 (2.30)
Contrast Enhancement Score						
Mean **SD**	0.01 (0.20)	3.11 (2.52)	0.0 (0.15)	3.73 (2.67)	0.01 (0.13)	2.95 (2.44)

2.3.2. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Except for the QT_C study, no response endpoints were measured in clinical pharmacology studies.

2.3.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The only known active moiety is the parent compound. According to the applicant, Dotarem does not undergo any metabolism and is excreted exclusively as parent. However, there is no direct data for such a claim. For all samples, plasma and urine samples were processed using nitric acid and hydrogen peroxide (destroying any dissociation products or metabolites present in the samples) and total gadolinium content was measured.

2.4. Exposure-Response
2.4.1. What are the characteristics of the exposure-response relationship for effectiveness?
2.4.2. What are the characteristics of the exposure-response relationships for safety?

No exposure-response relationships were determined.

2.4.3. Does this drug prolong QT/QTc Interval?

In the pre clinical studies performed *in vitro* (purkinje fiber) and *in vivo* (several studies on normal and sensitized animals), there was "no signal of any potential of Dotarem to induce QT/QTc prolongation."

The ECG safety of Dotarem has been evaluated in 18 patients during two controlled clinical trials performed by the applicant (study **DGD-3-6**: 6 patients; study **DGD-3-28**: 12 patients). No abnormalities were found. In addition, the pharmacokinetic study **(DGD 44-039)** involved 40 patients suffering from cardiac disease for which a contrast-enhanced T 1 MRI examination was required. Patients received two doses (0.1 mmol/kg followed by a 2X dose of 0.2 mmol/kg) of Dotarem and 11 ECGs were performed for each patient for each period. The applicant states, that Dotarem showed "no effect" on QT or QTc interval or other ECG parameters. QT and QTc values greater than 450 ms were observed in 6 patients (3 patients presented these values under both treatments and 3 under Dotarem only). Of the 3 patients under Dotarem, one 25-year-old female patient presented such an isolated QT associated with bradycardia, one 55 year-old male patient presented an isolated QTcB associated with an important increase of heart rate from baseline and one 47-year-old female patient, who already presented QTc values above 440 ms during the placebo period, presented an isolated QT and QTc after Dotarem. Increases of QTcB above 30 ms were observed in 7 patients, 4 under placebo and 3 under Dotarem (the maximal increase observed under Dotarem being +43.7 ms in the previously mentioned 55-year-old male patient).

Additional review of the human QT_C data has been consulted to the CDER Interdisciplinary Team for QT studies (the IRT).

2.4.4. Is the dose and dosing regimen selected consistent with the known E-R relationship?

No dose finding study was conducted and no exposure-response relationship was determined.

2.5. Pharmacokinetics
2.5.1. What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

The applicant conducted a PK study in healthy male and female subjects in which one cohort received a single dose of 0.1 mmol/kg, and a second cohort received two doses: an initial dose of 0.1 mmol/kg and a subsequent dose (20 min after the initial dose) of 0.2 mmol/kg after. This dosing pattern was investigated to provide, in part, information on a potential clinical scenario of a first dose resulting in unsuccessful imaging.
Plasma samples were collected at,
Group A: 0 (prior to dosing) and at the end of the injection, then at 5 min, 10 min, 20 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h and 48 hours after dosing,
and
Group B: 0 (prior to dosing) and at the end of the 1st injection, then at 5 min, 10 min and 18 min (just before the 2nd injection), and at the end of the 2nd injection and at 25 (5 min after the 2nd dosing), 30 (10 min after the 2nd dosing), and 45 min after the 1st dosing then at 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h and 48 hours after the first dosing.
Urine samples were collected at,
0 (prior to dosing) and then during the intervals 00-02, 02-04, 04-06, 06-12, 12-24 and 24-48 hours after dosing.

The PK parameters for the two dose groups are shown in **Figure 1.** and **2.** and **Table 4.** and **Table 5.** The results showed that the overall exposure to Gd-DOTA is dose proportional. The mean AUC in Group B after a total dose of 0.30 mmol/kg is about three times higher than the mean AUC in Group A (0.10 mmol/kg). The mean maximal plasma concentration measured in Group B after the second administration of 0.2 mmol/kg dose was about two times higher than the mean maximal plasma concentration measured after the first 0.10 mmol/kg dose. The elimination half-life after a cumulative triple dose is similar to that obtained after the single 0.1 mmol/kg dose in this trail, and similar to that observed in other trials.

Figure 1. Mean and SD plasma concentration versus time profiles of Gd-DOTA – Group A (0.10 mmol/kg)

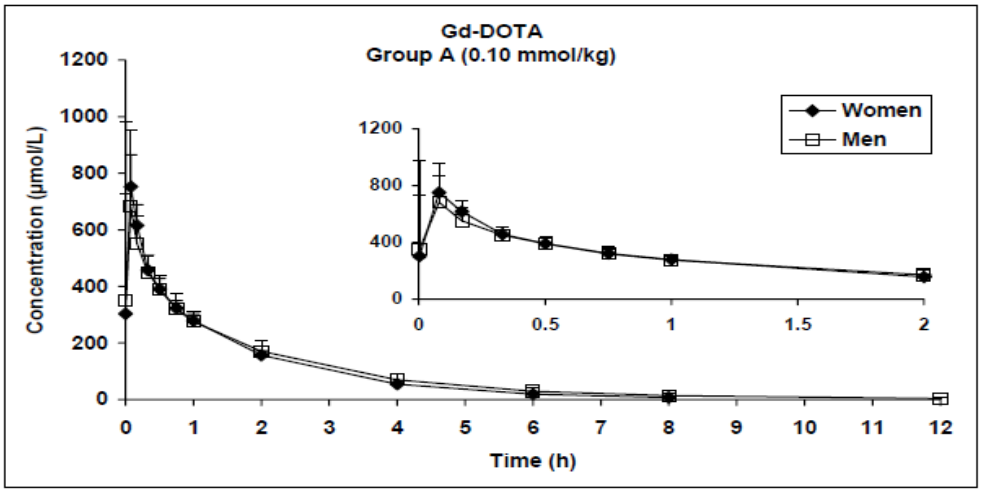


Figure 2. Mean and SD plasma concentration versus time profiles of Gd-DOTA – Group B (0.10 + 0.2 mmol/kg)

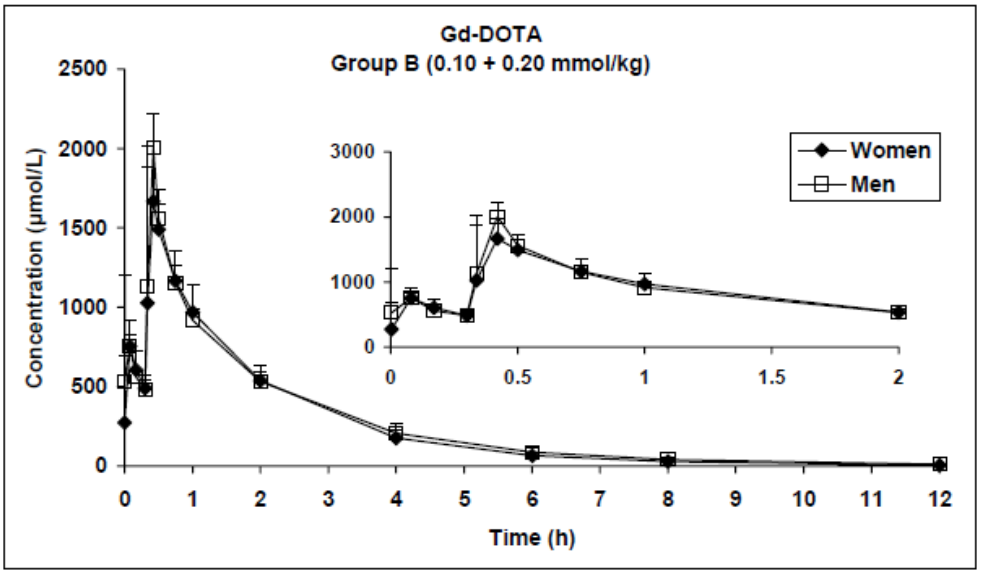


Table 4. Pharmacokinetic properties of Dotarem after injection of 0.1 mmol/kg

Group A (0.10 mmol/kg)	Women (N=8)	Men (N=8)	Gender effect
Dose (µmol)	6188 (704)	7375 (518)	-
C_{max} (µmol/L)	799.03 (192.63)	836.85 (451.02)	NS (1)
t_{max}* (min)	5.00 (0.10 - 10.00)	5.00 (0.11 - 10.00)	NS (2)
AUC_{0-t} (h*µmol/L)	953.51 (76.22)	1038.74 (240.46)	NS (1)
$AUC_{0-\infty}$ (h*µmol/L)	970.72 (73.34)	1061.16 (239.24)	NS (1)
C_{max}/dose (µmol/L)	0.129 (0.030)	0.117 (0.072)	NS (3)
AUC_{0-t}/dose (h*µmol/L)	0.156 (0.021)	0.143 (0.042)	NS (3)
$AUC_{0-\infty}$/dose (h*µmol/L)	0.159 (0.022)	0.146 (0.042)	NS (3)
$t_{1/2}$ (h)	1.39 (0.18)	2.04 (0.72)	$p < 0.05$ (4)
MRT (h)	1.71 (0.22)	2.18 (0.32)	$p < 0.05$ (4)
Cl_T (mL/min)	107.05 (17.65)	121.88 (31.77)	NS (4)
Vd_β (L)	12.70 (1.36)	21.16 (8.59)	$p < 0.05$ (4)
Vd_{ss} (L)	10.87 (1.31)	15.65 (3.30)	$p < 0.05$ (4)
Cl_T (mL/min/kg)	1.74 (0.12)	1.64 (0.35)	NS (4)
Vd_β (L/kg)	0.210 (0.030)	0.284 (0.103)	NS (4)
Vd_{ss} (L/kg)	0.179 (0.026)	0.211 (0.035)	NS (4)
fe_{0-48h} (% of dose)	72.91 (17.03)	85.43 (9.67)	NS (4)
Clr (mL/min)	78.38 (22.90)	103.27 (25.72)	NS (4)
Clr (mL/min/kg)	1.27 (0.32)	1.40 (0.31)	NS (4)

*: Median (min-max) value
(1): Analysis of variance on log-transformed data
(2): Kruskal-Wallis test on natural data
(3): Analysis of variance on log-transformed and dose-normalised data
(4): Analysis of variance on natural data

Table 5. Pharmacokinetic properties of Dotarem after injection of 0.1 + 0.2 mmol/kg

Group B (0.10 + 0.20 mmol/kg)	Women (N=8)	Men (N=8)	Gender effect
Dose 1st IV (µmol)	6313 (530)	7125 (1217)	-
C_{max} 1st IV (µmol/L)	800.24 (237.59)	947.59 (410.18)	NS (1)
t_{max} 1st IV*(min)	5.00 (0.12-5.00)	5.00 (0.11-5.00)	NS (2)
C_{max} 1st IV/dose (µmol/L)	0.126 (0.033)	0.134 (0.059)	NS (3)
Dose 2nd IV (µmol)	12688 (961)	14188 (2478)	-
C_{max} 2nd IV (µmol/L)	1778.37 (453.60)	2166.33 (314.65)	-
t_{max} 2nd IV* (min)	25.00 (20.22 – 30.00)#	25.00 (20.22 – 25.00)#	-
Triple Dose (µmol)	19000 (1488)	21313 (3693)	-
AUC_{0-t} (h*µmol/L)	2897.45 (490.31)	3054.66 (356.10)	NS (1)
AUC_{0-t}/dose (h*µmol/L)	0.152 (0.022)	0.146 (0.023)	NS (4)
$t_{1/2}$ (h)	1.69 (0.29)	1.87 (0.17)	NS (5)
fe_{0-48h} (% of dose)	85.54 (13.22)	91.95 (12.00)	NS (5)

*: Median (min-max) value
#: time relative to the first administration
(1): Analysis of variance on log-transformed data
(2): Kruskal-Wallis test on natural data
(3): Analysis of variance on log-transformed data (normalised by 1st IV dose)
(4): Analysis of variance on log-transformed data (normalised by Triple Dose)
(5): Analysis of variance on natural data

2.5.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Patient pharmacokinetic data was not included in the NDA.

2.5.3. What are the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

The inter- and intra-subject variability of the PK parameters in volunteers and patients with target disease was not reported.

2.5.4. What are the characteristics of drug absorption?

Dotarem is administered as a single-time intravenous injection. The characteristics of drug absorption from alternate routes are not reported.

2.5.5. What are the characteristics of drug distribution?

The volume of distribution (11 L in women and 16 L in men) approximates extracellular interstitial space. *In vitro* protein plasma binding was less than 4%.

2.5.6. Does the mass balance study suggest renal or hepatic as the major route of elimination?

Formal mass balance study results are not reported. After a single intravenous injection of 0.1 mmol/kg to healthy subjects, 86.6±10.3 % of the Gd dose was recovered in urine over 48 h (Study DGD 3-6). The applicant states that free gadolinium, if occuring, would be phagocytosed by liver and released very slowly over an extended period of time.

2.5.7. What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?
2.5.8. What are the characteristics of drug metabolism?

I*n vitro* investigation of drug metabolism is not reported.

The applicant repeatedly states that Dotarem does not undergo metabolism and is excreted as a parent. There is no direct evidential data for such a claim. In all analytical methods for measurement of gadolinium, an ICP/OES method was used. The plasma or urine samples were processed using nitric acid and hydrogen peroxide and total gadolinium content was measured. An IR was sent to the applicant to provide evidence that the parent was excreted in urine. PK of the drug and its relevant metabolites were not reported for patients.

2.5.9. Is there evidence for excretion of parent drug and/or metabolites into bile?
2.5.10. Is there evidence for enterohepatic recirculation for parent and/or metabolites?

There is not evidence for enterohepatic recirculation for parent and/or metabolites. Data following non-IV administration is not reported.

2.5.11. What are the characteristics of drug excretion in urine?

After a single intravenous injection of 0.1 mmol/kg to healthy subjects, 86.6±10.3 % of the Gd dose was recovered in urine over 48 h (Study DGD 3-6). The healthy subject results from the renal impairment trial (DGD 3-28) showed that almost all urine excretion occurred during the first 24-h (93.3%±4.7% of the dose injected)**.**

2.5.12. Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

As discussed in 2.5.1., PK was dose proportional between doses of 0.1 mmol/kg and 0.2 mmol/kg.

2.5.13. How do the PK parameters change with time following chronic dosing?

Dotarem is generally administered as a single dose; perhaps as needed, repeat dosing could occur (see 2.5.1.). Investigation of chronic dosing was not part of drug development

2.5.14. Is there evidence for a circadian rhythm of the PK?

There is not evidence for a circadian rhythm of the PK, but only limited concentration-time data are reported, and data are not reported by time-of-day.

2.6. Intrinsic Factors
2.6.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

The role of intrinsic factors in contributing to inter-subject variability was not explored.

2.6.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?
2.6.2.1. Severity of Disease State
2.6.2.2. Body Weight
2.6.2.3. Elderly

The E-R relationship is unknown, and PK data were not collected in patients.

2.6.2.4. Pediatric Patients
The E-R relationship is adults as well as pediatric patients is unknown.

The applicant conducted three pilot trials of Dotarem in pediatric patients. There were 38 children enrolled in the primary efficacy trial (Study DGD-50). However, no PK data were collected in any of these four studies. The applicant is seeking an indication for all pediatric patients (no lower age limit). Across the four trials, there were only seven patients studied that were under two years of age.

We recommend a post-marketing requirement that the applicant conduct a pharmacokinetic study (including collection of excreta) comparing the time profiles of subjects under two year old to adults. Bioanalysis should include determination of whether Gd-containing moieties other than parent are excreted. If such moieties are present, they should be quantified in excreta, and if reasonable, in plasma. The results of this trial may show that subjects under two have profiles dissimilar to adults. If this result occurs, it may prompt an additional requirement to acquire safety and imaging data in children under two, possibly at a dose or doses other than 0.1 mmol/kg.

2.6.2.5. Race/Ethnicity

The E-R relationship is unknown, and PK data were not collected in patients.

2.6.2.6. Renal Impairment

Results from subjects with renal impairment receiving a single 0.1 mmol/kg dose (the standard clinical dose) are presented in **Table 6.**

Table 6. Pharmacokinetic parameters in healthy volunteers and in patients with renal impairment.

	Non-impaired	**Moderate** (CL_{CR} 30 – 60 mL/min)	**Severe** (CL_{CR} 10 – 30 mL/min**)**
AUC (μmol*hr/L)	870 ± 80	3013 ± 645	8122 ± 665
Cmax observed (Tmax = X min or Y min) (umol/mL)	551 ± 70	591 ± 25	671 ± 97
T1/2 (hr)	1.6 ± 0.2	5.1 ± 1.0	13.9 ± 1.2
CLTot (hr)	108.3 ± 7.8	40.0 ± 8.8	13.8 ± 0.6
Distribution volume (L/kg)	0.246 ± 0.03	0.236 ± 0.01	0.234 ± 0.01
Gd excreted (% dose) in 24 h	93.3 ± 4.7	75 ± 5	48.6 ± 4
Gd excreted (% dose) in 48 h	Not reported	76.9%±4.5%	Not reported
Total Gd excreted (% dose) (72 h collection)	Not reported	Not reported	68.4 ± 3.5

In non-impaired subjects, almost all contrast agent was eliminated in the urine during the first 24-h (93.3%±4.7% of the dose injected). In moderately-impaired subjects, the mean percentage elimination was 75%±5% of the dose injected 24 h post Dotarem and 76.9%±4.5% at 48 h post Dotarem. In severely-impaired subjects, this percentage was decreased to 48.6%±4% 24 h post Dotarem and 68.4%±3.5% 72 h post Dotarem.

These findings raise the question of whether dose adjustments should be recommended for patients with renal impairment. The reviewer is of the opinion that dose adjustment is unwise. Efficacy of the drug (imaging) is unlikely to be related to AUC. Rather, effective imaging is related to the concentration at the time of imaging, which is shortly post-administration. The lowering of dose would result in lowering early concentrations and therefore risks compromising imaging results. From a safety perspective,

1. gadoterate causes very limited adverse events
2. other approved GBCAs, which also show dramatic increases in AUC in those with renal impairment, do not have recommendations for dose adjustment for renal impairment

3. gadoterate has very high thermodynamic and kinetic stability: while *in vivo* stability was not assessed, the apparent likelihood of free Gd, which might be a safety risk, is less for gadoterate than the other GBCAs
4. Doatarem will receive class labeling (black box warning) for the risk of the life-threatening adverse event NSF (nephrogenic systemic fibrosis) in patients with severe renal impairment. The prescribing community (radiologists) are acutely aware of the risks of administering GBCAs to renal impairment patients. The use of GBCA in patients with renal impairment is almost non-existent due to legal liabilities (anecdotal communications from radiologists).

2.6.2.7. Hepatic Impairment

The effect of hepatic impairment on imaging or PK are not reported.

2.6.2.8. What pregnancy and lactation use information is available?

No pregnancy or lactation use information is available.

2.6.3. Does genetic variation impact exposure and/or response?

The effect of genetic variation impact on exposure and/or response is not reported.

2.7. Extrinsic Factors
2.7.1. Is there an in vitro basis to suspect in vivo drug-drug interactions?
2.7.2. Is the drug a substrate of CYP enzymes?
2.7.3. Is the drug an inhibitor and/or an inducer of enzymes?
2.7.4. Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

I*n vitro* investigation of drug metabolism is not reported.

2.7.5. Are there other metabolic/transporter pathways that may be important?

Metabolic/transporter pathways were not explored by the applicant.

2.7.6. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

The effect of extrinsic factors influence on exposure and/or response is not reported.

2.7.7. What are the drug-drug interactions?

No drug interaction studies conducted by applicant for Dotarem.

2.7.8. Does the label specify co-administration of another drug?

The package insert does not specify co-administration of another drug.

2.7.9. What other co-medications are likely to be administered to the target population?
2.7.10. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

There is no mechanistic basis for PD drug-drug interactions.

2.8 General Biopharmaceutics
2.8.1. Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?
2.8.2. How is the proposed to-be-marketed formulation linked to the clinical service formulation?
2.8.2.1. What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?
2.8.2.2. If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?
2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?
2.8.4. Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?
2.8.5. If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

Dotarem meglumine is an intravenously administered simple aqueous solution. There were no changes in formulation during clinical development. The above biopharmaceutics questions are not applicable.

2.9. Analytical Section
2.9.1. How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?
2.9.2. Which metabolites have been selected for analysis and why?
2.9.3. For all moieties measured, is free, bound, or total measured?
2.9.4. What bioanalytical methods are used to assess concentrations of the measured moieties?
2.9.5. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?
2.9.5.1. What are the lower and upper limits of quantitation?
2.9.5.2. What are the accuracy, precision, and selectivity at these limits?
2.9.5.3. What is the sample stability under conditions used in the study?
2.9.5.4. What is the plan for the QC samples and for the reanalysis of the incurred samples?

The analytical validated method consisted of mineralization of biological samples with Nitric Acid (HNO_3), and Hydrogen Peroxide (H_2O_2) and analysis by ICP/OES (Inductively Coupled Plasma/Optical Emission Spectroscopy). Thus, total Gd was the moiety measured. The method was linear from 5.00 µmol/L to 2000.00 µmol/L in plasma and from 10.00 to 5000.00 µmol/L in urine.

The in-process performance of the bioanalytical methods were not reported for Studies DGD-3-06 and DGD-03-28. The results of the in-process quality control samples for study DGD-3-48 are shown in **Table 7.** These results for Study DGD-3-48 are satisfactory.

Table7. Performance of the in-process quality control samples for study DGD-3-48

Run	Matrix	%Nominal (Mean)	%Nominal (St Dev)	LLQ (umol/L)	ULQ (umol/L)	> 15% from nominal
1	Plasma	108.1	6.94	5	2000	n=1 nominal = 1600 measured = 1891 (118%)
2	Plasma	106.08	7	5	2000	n=1 nominal = 1000 measured = 805.7 (119%)
1	Urine	110.59	6.72	10	5000	n=1 nominal = 2500 measured = 2985 (119%)
2	Urine	105.29	4.27	10	5000	None

3. Detailed Labeling Recommendations

The reviewer's recommendations for edits to portions of Sections **7 DRUG INTERACTIONS, 8 USE IN SPECIFIC POPULATIONS** and **12 CLINICAL PHARMACOLOGY** begin on the next page. The applicant's proposed package insert (original, annotated) is included as **Appendix 4.1**

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page.

4. Appendices

4.1. Applicant's Proposed Package Insert (original, annotated)

4.2. Cover sheet and OCPB Filing/Review Form

Appendix 4.1. Applicant's Proposed Package Insert (original, annotated)

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix 4.2. Cover sheet and OCPB Filing/Review Form

4 Pages of NDA Filing and Review Form has been removed. A duplicate of this NDA Filing and Review Form dated 11/14/12 can be found in this review

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
02/20/2013

GENE M WILLIAMS
02/20/2013

BRIAN P BOOTH
02/20/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review - Premarket

Date:	January 7, 2013
Reviewer(s):	Michael E. Kieffer, Pharm.D., M.A., Division of Pharmacovigilance II Joseph M. Tonning, M.D., R.Ph., M.P.H., Division of Pharmacovigilance II
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Product Name(s):	Dotarem (gadoterate meglumine)
Subject:	All Adverse Events
Application Type/Number:	NDA 204781
Applicant/Sponsor:	Guerbet
OSE RCM #:	2012-2735

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Division of Medical Imaging Products (DMIP) requested that the Division of Pharmacovigilance II (DPV II) summarize postmarketing reports associated with the use of Dotarem found within the FDA Adverse Event Reporting System (FAERS) database and the medical literature in both adult and pediatric patients (0 to 17 years of age), including patients aged less than two years. If Dotarem receives approval, it will be the first GBCA indicated in the U.S. for patients aged less than two years.

As of November 27, 2012, the FAERS database contained 51 cases associated with Dotarem (4 pediatric or 8% and 47 adult cases). There were no reports of pediatric deaths or NSF cases in the pediatric population. The pediatric cases consisted of one case each of: accidental overdose (without adverse event); premature birth (most likely not related to Dotarem use); heart rate decreased; and hypersensitivity reaction. Hypersensitivity reactions are described in the proposed Dotarem label's Warnings and Precautions section and bradycardia is listed in the Postmarketing Experience section.

The majority of reported adverse events in the 47 adult cases are already included within the proposed Dotarem labeling to include: hypersensitivity reactions (n=22); NSF (n=10; all confounded); coma (n=1); convulsions (n=1); dizziness (n=1); fever and chills (n=1); and loss of consciousness (n=2). The remaining cases either reported related terms in the proposed labeling or were confounded by multiple drugs and/or underlying disease. These cases included: acute renal failure (n=3); thrombosis (n=2); acute cholestatic hepatitis with acute renal failure (n=1); agranulocytosis (n=1); intrathecal administration/medication error (n=1); and vagal reaction (n=1).

A review of the literature did not elicit concerns of adverse events in children less than 2 years of age exposed to Dotarem. A PubMed search conducted on December 5, 2012, retrieved 13 articles with titles and abstracts related to the use of Dotarem in the pediatric population, eight of the articles addressing patients aged less than two years. The articles included approximately 1,203 pediatric patients administered Dotarem with about 177 of these patients aged less than two years. None of the articles mentioned specific adverse events in any of the pediatric patients studied.

This review did not identify any new safety issues with Dotarem in either pediatric or adult populations. However, since the data provided from FAERS is limited with respect to quantity of reports, the appropriate final labeling for Dotarem should be made based on all available data to the Review Division.

1 INTRODUCTION

1.1 BACKGROUND

Dotarem is an ionic macrocyclic gadolinium-based contrast agent (GBCA). The NDA was submitted on September 20, 2012, and the PDUFA action date is March 20, 2013. Dotarem's sponsor, Geurbet, is requesting United States marketing approval for the indication of intravenous use for magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonates to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. No other GBCAs currently marketed in the US have been approved for use in children aged less than two years. A concern in this age group is that the reduced renal function of this patient population, compared to patients aged greater than 2 years, would lead to Dotarem retention and predispose them to the development of nephrogenic systemic fibrosis (NSF). Dotarem injection will contain 376.9 mg/mL gadoterate meglumine (equivalent to 0.5 mmol/mL) when marketed, and will be available in vial and prefilled syringe.[1]

1.2 REGULATORY HISTORY

Dotarem is not currently approved for marketing in the United States. Thus, there is no requirement for the sponsor to submit postmarketing safety reports to the Agency. Dotarem's first global marketing approval was in France in 1989. Since then it has obtained marketing approval in many countries in Europe, Asia, Central and South America, and Africa. Using data collected from Europe, South Korea, Taiwan, Mexico, and Brazil and based on a 0.27% usage rate in France for children aged less than two years, the manufacturer estimates that 51,000 children (aged less than two years) have received Dotarem between 2005 and 2012. Based on the total liters of Dotarem sold and a formula based on normal doses and projected percentages of use for each indication, the sponsor estimates 30,532,599 people have received Dotarem since its first global marketing approval.[2]

Dotarem has been investigated in 23 studies (n=1,329; United States proposed indication) involving magnetic resonance imaging (MRI) in patients with CNS lesions, suspected brain tumors or metastases, Alzheimer's disease, and for other neurological reasons. Three of these studies (DGD-3-15, DGD-3-16, and DGD-3-29) were specific for pediatric patients (n=141 children). Seven patients aged less than 2 years were included in these pediatric studies. Only one adverse effect was reported from these seven patients, which was vomiting determined by the study physician as unrelated to the Dotarem. Six postmarketing surveillance studies (n=234) were also conducted in children aged less than two and no related adverse effects were reported. The most common adverse reactions for all clinical trails involving Dotarem were nausea, headache, injection site pain, injection site coldness, and burning sensation.

1.3 PROPOSED PRODUCT LABELING

[1] Proposed Dotarem Label - revision date currently not provided.
[2] Integrated Safety Study, Dotarem, version 1, dated August 26, 2012.

The proposed labeling for Dotarem has the following information concerning the pediatric population:

Adverse Reactions in Children **(Section 6.1 of proposed label)**

During clinical trials, 141 children (7 aged < 24 months, 33 aged 2-5 years, 58 aged 6-11 years and 43 aged 12-17) received DOTAREM. Overall, 6 children (4.3%) reported at least one adverse reaction following DOTAREM administration. The most frequently reported adverse reaction was headache (1.5%). Most adverse events were mild in severity and transient in nature, and all patients recovered without treatment.

Overall, in 241 children aged < 2 years old, from 6 post marketing studies (234 children) and 3 clinical trials (7 children), there were no adverse reactions reported.

Adverse Reactions in Children

Adverse events related to DOTAREM are uncommon in children. The expectedness of these events is similar to that of the events reported in adults.

Pediatric Use **(Section 8.4 of label)**

The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg have been established in children from neonates to 17 years of age. No dosage adjustment is necessary in this population.

Use of DOTAREM in children is supported by evidence from both adequate and well-controlled studies and post marketing studies.

See Appendix A for proposed labeling regarding Dotarem use in pregnancy and during lactation.

Proposed Boxed Warning

WARNING: NEPHROGENIC SYSEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs.

The risk of NSF appears highest among patients with:

- Chronic, severe kidney disease (GFR ,30 mL/min/1.73m^2), or
- Acute kidney injury.

Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 year, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1).

For patients at risk for NSF, do not exceed the recommended DOTAREM dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration [see Warnings and Precautions (5.1)]

Proposed Warnings AND PRECAUTIONS

Hypersensitivity Reactions

Prior to DOTAREM administration, assess all patients for the risk for hypersensitivity reactions to contrast media, bronchial asthma, or other allergic disorders.

Anaphylactic and anaphylactoid reactions have been reported with DOTAREM, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of DOTAREM administration and resolved with prompt emergency treatment [see Adverse Reactions (6)].

See Appendix B for Warnings and Precautions for Nephrogenic Systemic Fibrosis, proposed Adverse Reactions section, and proposed Postmarketing Experience label section.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	November 27, 2012
Time period of search	January 1, 1969 (Database Initiation) – November 27, 2012
Product Terms	Product Name: Dotarem Active Ingredient: gadoterate meglumine; gadoteric acid

*See Appendix C for description of the FAERS database.

2.2 LITERATURE SEARCH

The medical literature was searched with the strategy described in Table 2.

Table 2. Literature Search Strategy	
Date of search	December 5, 2012
Database	PubMed
Search Terms	Gadoterate
Years included in search	All years
Languages	All languages searched
Other criteria	Text strings: "pediatric," "children, and "infant"

3 RESULTS

3.1 FAERS REPORTS

The FAERS search retrieved 54 reports, which included 3 duplicate reports. Table 3 below summarizes the 51 cases included in this case series.

Appendix D lists all the AERS case numbers, AERS ISR numbers and Manufacturer Control numbers for the 51 cases (three duplicates removed) in this case series.

Table 3. Total number of FAERS reports (N=51; search from 1969 to November 27, 2012)

	All reports	Serious[‡]	Death
Adults (≥17 years)	41	41	1
Pediatrics (0-17 years)	4	4	0
Age unknown (null values)	6	6	0[†]
Total	51	51	1

[‡] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

3.2 PEDIATRIC CASES REPORTED IN FAERS (N-4)

Table 4 summarizes the four FAERS cases from the Pediatric Case Series with Dotarem.

Table 4. Descriptive characteristics of Pediatric Case Series from January 1, 1969 to November 27, 2012

		(N=4)
Age	0 – 1 month	1
	1 month - <2 years	2
	2-5 years	0
	6-11 years	1
	12-17 years	0
Sex	Male	2
	Female	2
Country of reporter	Foreign	4
	France	3
	Germany	1
Report type	Expedited	4
Event date	2007	1
	2008	1
	2009	2
Dose (n=3)	Dose 1	16mL(overdose)
	Dose 2	6 mL
	Dose 3	2 mL

Table 4. Descriptive characteristics of Pediatric Case Series from January 1, 1969 to November 27, 2012 (N=4)		
Indications (n=2)	Cranial CT	1
	MRI	1
Serious Outcomes*	Hospitalized	4
MedDRA Preferred Terms (PTs)±	Accidental overdose	1
	Cough	1
	Foetal growth restriction	1
	Heart rate decreased	1
	Hypersensitivity	1
	Oropharyngeal discomfort	1
	Small for dates baby	1
	Premature baby	1

*Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
± Case may contain more than one PT

No pediatric deaths were reported in this case series. No NSF cases were reported in pediatric patients within this case series. Below is a summary of the 4 pediatric cases:

Case # 6553744 (Germany). A 16 month-old male infant (weighing 10 kg) with no known allergies and no prior examinations with contrast media underwent a cranial computerized tomography study with Dotarem for first imaging and clarification of the symptom complex associated with neurofibromatosis type 1. Dotarem was administered manually and resulted in an accidental overdose of 16 milliliters (proposed label recommends 0.1 mmole/kg or 0.2 mL/kg of body weight). The infant was hydrated, his fluid intake and output monitored, and was admitted to the intensive care unit for monitoring purposes. Ultimately, no adverse events were reported as a result of the overdose.

Case # 7246205 (France). A female baby (weighing 1.27 kilograms) was delivered by cesarean section without neonatal defect, but prematurely at 31.5 weeks of gestation. The premature delivery was required due to the occurrence of preeclampsia in the mother resulting in fetal growth retardation. The mother received a magnetic resonance imaging study using Dotarem (dose not reported) as contrast at approximately two weeks into her pregnancy. The pregnancy was further complicated by the following factors: (1) the mother initially tried to abort the pregnancy with emergency contraceptive pills (Norlevo), (2) the mother had a history of hypertension treated with atenolol (continued during pregnancy with the dose doubled starting at the sixth month of pregnancy), and (3) the mother was diagnosed with multiple sclerosis treated with steroids during the fifth and six weeks of her pregnancy. The child was lost to follow-up and no further data is known.

Case # 7332885 (France). An 11 month-old male child received a magnetic resonance imaging (MRI) study with 2 mLs of Dotarem as contrast. The patient received four patches of EMLA (lidocaine, prilocaine) to the elbow fold and hand for anesthesia prior to catheter insertion. During the MRI, the child's heart rate decreased from 110 beats per minute (bpm) to 65 bpm 40

minutes later. He appeared pale and the MRI was stopped. Within a few minutes of stopping the MRI, his heart rate recovered without corrective treatment, and he recovered without sequelae.

Case # 6444840 (France). An eleven year old female, with a history of a previous well tolerated Omniscan administration, received 6 mLs of Dotarem and experienced an allergic reaction with dry cough and pharyngeal discomfort. She was treated with an injection of polaramine (dexchlorpheniramine). She recovered without sequelae.

PEDIATRIC CASE SUMMARY

There is no evidence from these 4 cases that there are new pediatric safety concerns with Dotarem at this time, including any safety concerns in patients aged less than 2 years.

3.3 PEDIATRIC LITERATURE REVIEW

PubMed was searched on December 5, 2012 for the MeSH term "gadoterate." This term alone was searched to ensure as broad a search as possible, so that all articles coded with the "gadoterate" MeSH term were retrieved. This search retrieved 707 articles (all years and all languages). To comply with the request from DMIP to review literature in the <2 year-old age group, the titles and abstracts of these 707 articles were searched for the following text strings: "pediatric," "children, and "infant."

From this text string search, 13 relevant articles in English were retrieved (Appendix E). Of these 13 articles, only 8 mentioned gadoterate use in patients < 2 years of age. However, for completeness, 5 additional references[3] are included in Appendix E because these references mention gadoterate use in older pediatric patients > 2 years of age.

Of these 13 references, all *except the first reference* (Emond and Brunelle) mention gadoterate in the context of its use as a diagnostic agent in a small number of pediatric patients. No specific adverse events are mentioned among these small patient groups. However, the first reference article in Appendix E (the Emond and Brunelle article) describes a larger post-marketing study of 104 neonates and infants who received gadoterate in a single pediatric hospital in France. This first reference is discussed separately below.

Emond S, Brunelle F. Gd-DOTA administration at MRI in children younger than 18 months of age: immediate adverse reactions. Pediatr Radiol. 2011 Nov;41(11):1401-6. Epub 2011 Jul 24. (PMID 21786126)

This French post-marketing study was an observational, non-randomized, single-center, open-label study. This study included 104 infants and neonates with an age range of 3 days to 18 months. The aim of the study was to gain further knowledge on the safety of gadoterate in children less than 18 months of age in routine clinical practice. Thus, adverse events were specifically being monitored. A standardized questionnaire was used to collect patient

[3] In Appendix E: Secinaro et al (Reference 3); Merlini et al (Reference 5); Sebag et al (Reference 9); Hervé-Somma et al (Reference 12); and Romero et al (Reference 13)

information. Variables recorded for each child included but were not limited to: demographics (age, sex, weight); risk factors for contrast agent reactions; volume of gadoterate administered; and overall tolerance to gadoterate.

The volume of gadoterate injected per child ranged from 0.6 ml in a newborn (male, 3 days, 3 kg) to 4 ml in the heaviest/oldest child (female, 18 months, 20 kg), with a median of 2 ml. The children were observed in the hospital for at least 2 hours after gadoterate administration. No adverse events were reported among these children.

The authors stated, "We believe that our data are of significant clinical and research utility for centers assessing children with central nervous system disorders by MRI. Possible limitations of such studies are the small number of included patients and technical difficulties using MRI in children. Clinical trials in children are more challenging than those in adults." The authors further stated, "Although difficult to conduct, more extensive clinical studies are warranted to assess long-term safety."

This article mentioned two other references not retrieved by the PubMed search previously described. These 2 articles are summarized below.

Briand Y, Neiss AC, Vitry A (1992) Efficacy and safety of the macrocyclic complex Gd-DOTA in children: results of a multicentre study. In: 29th congress of the European Society of Pediatric Radiology, Budapest: R12.

This study does not appear in PubMed and has not been published to our knowledge. However, the Emond article, when referring to this study, states "Our study, conducted in France, included 402 patients (81% of the children were 15 years old or younger and 6.5% were 2 years old or younger). Our results confirmed the advantages of Gd-DOTA [gadoterate] injection in children as well as its favorable safety profile in terms of immediate adverse reactions."

Herborn CU, Honold E, Wolf M, Kemper J, Kinner S, Adam G, Barkhausen J. Clinical safety and diagnostic value of the gadolinium chelate gadoterate meglumine (Gd-DOTA). Invest Radiol. 2007 Jan;42(1):58-62.

The purpose of this study was to assess the diagnostic value and safety of gadoterate. A total of 24,308 patients were intravenously injected with gadoterate for various diagnostic examinations. Demographic, clinical, imaging, and safety data were obtained from board certified radiologists in 61 radiologic institutions throughout Germany between January 2004 and October 2005. Patient data were collected through the use of standardized questionnaires completed by the radiologist.

A detailed breakdown of patient age was not provided for the 24,308 patients studied. Regarding ages of the patients, the article has only this passing statement: "Patients ranged in age from a few weeks to 103 years (mean, 51.8 years)." However, the Emond article references this Herborn study and states that in the Herborn study "2.7% of the children were 18 years old or

younger and 0.008% were 2 years old or younger." Emond further states that in the Herborn study, "Out of 24,000 patients, the overall incidence of reported adverse events was only 0.4%: one serious adverse event (anaphylactic shock) occurred in an adult patient and no adverse event in children younger than 2 years of age." The Herborn article confirms that adverse events were reported in 0.4% (n = 94) patients, but there is no breakdown by patient age. Herborn further states that of the 24,308 patients, 1 patient (0.004%) developed a serious adverse event considered to be life threatening. This event, anaphylactic shock, occurred in a 65 year-old man, confirming statements made by Emond when referring to the Herborn article that no adverse events occurred in pediatric patients.

3.4 ADULT CASES REPORTED IN FAERS (N=47)

Table 5 summarizes the 47 cases reported in adults in the FAERS database.

Table 5. Descriptive characteristics of Adult Case Series from January 1, 1969 to November 27, 2012 (47=number in case series)

Age (n=42) (Years)	Mean	52.6
	Median	50
	Range	18 to 78
Sex	Male	24
	Female	23
Country of reporter	Foreign:	47
	France	16
	Germany	8
	Chile	5
	Belgium	4
	Denmark	3
	Italy	3
	Great Britain	2
	Japan	2
	Argentina	1
	Netherlands	1
	Singapore	1
	Spain	1
Report type	Expedited	47
Event date	2002	1
	2003	2
	2004	6
	2005	6
	2006	5
	2007	6
	2008	3
	2009	6
	2010	2

Table 5. Descriptive characteristics of Adult Case Series from January 1, 1969 to November 27, 2012 (47=number in case series)		
	2011	1
	2012	1
	Unknown	8
Serious Outcomes*,±	Death	1
	Life-threatening	10
	Required Intervention	9
	Hospitalized	47
	Disability	8
	Other serious	10

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
± There may be more than one outcome per case.

Nephrogenic Systemic Fibrosis (n=10; Fatal [n=1], Non-fatal [n=9])

NSF is labeled within the proposed Dotarem label (Boxed Warnings). In nine of the ten cases, the patients have a history of chronic renal failure prior to the Dotarem exposure with one case not reporting a renal status (see Case # 8900191 below). Determination of causality is confounded by the administration of at least one other concomitant gadolinium contrast agent in all ten cases. Three case summaries are included in Appendix F. Appendix F also includes an outline of all 10 ten cases of nephrogenic systemic fibrosis.

Hypersensitivity Reactions (n=22)

Hypersensitivity is labeled within the proposed Dotarem label (Warnings and Precautions section). Of the cases identified as describing hypersensitivity reaction within the adult case series, 14 patients were female and nine were male. The average age was 53.5 years (n=20), median age was 52 years, and the age range was 33 to 78 years. The outcome in all 22 cases was coded as serious. Four cases were coded with a preferred term (PT) referring to shock (anaphylactic shock-3; cardiogenic shock-1). Two cases were coded with the PT laryngeal edema, and one each was coded with the PT pharyngeal edema and angioedema. Six cases were coded with loss of consciousness (PT). Five representative cases are described in the Appendix G. Appendix G also includes an outline for all 22 cases grouped as hypersensitivity reactions.

Appendix H contains the case summaries for the remaining labeled events (n=6) of coma (n=1); convulsions (n=1); dizziness (n=1); fever, chills (n=1); and loss of consciousness (n=2).

Appendix I contains case summaries for the unexpected events in adults (n=9) occurring following Dotarem administration: acute renal failure (n=3); acute cholestatic hepatitis with acute renal failure (n=1); thrombosis (n=2); agranulocytosis (n=1); intrathecal administration (n=1); and vagal reaction (n=1).

SUMMARY OF ADULT CASE SERIES

The FAERS search identified 47 adverse event reports (all coded as serious) associated with adult patients. The majority reported adverse events within the proposed Dotarem labeling (38/47, 81%) to include: hypersensitivity reactions (n=22); NSF (n=10; all confounded); coma (n=1); convulsions (n=1); dizziness (n=1); fever and chills (n=1); and loss of consciousness (n=2). Reported "unlabeled" adverse events (all coded as serious) include: acute renal failure (n=3; blood creatinine increase is labeled); thrombosis (n=2; superficial phlebitis is labeled); acute cholestatic hepatitis with acute renal failure (n=1); agranulocytosis (n=1); intrathecal administration/medication error (n=1); and vagal reaction (n=1; bradycardia labeled). These "unlabeled" and "unexpected" terms are not *specifically* listed in the proposed Dotarem labeling; however, many of these events will be described by related terms that will be contained in the proposed label.

4 DISCUSSION/CONCLUSION

The FAERS case series contained 51 cases: four pediatric patients aged less than or equal to 17 years (three aged less than two years) and 47 adult patients. The pediatric literature search identified 13 articles that reported studying about 1,203 pediatric patients, of which around 177 were aged less than two years. Neither the FAERS nor the literature reviews identified any new safety signals with Dotarem in the pediatric population. There were no deaths or NSF cases in the pediatric case series.

The most commonly reported adverse event in the adult case series were those related to hypersensitivity reactions (n=22). NSF was the next most frequently reported adverse event reported in adults (n=10). All cases of NSF associated with Dotarem use were confounded by co-administration of at least one other GBCA agent. Although there were nine cases that reported adverse events that are not listed in the proposed Dotarem labeling (unexpected), many of these events have related terms that will be contained in the proposed label (i.e., blood creatinine increase for acute renal failure n=3 (GBCAs are labeled for acute kidney injury [class labeling recommended by prior OSE review[4]]), superficial phlebitis for thrombosis n=2, and bradycardia for vagal reaction n=1). The remaining three unexpected adverse reactions reported with Dotarem were single reports of a medication error due to intrathecal administration, hepatitis/renal failure, and agranulocytosis, The latter two cases were both confounded by the administration of multiple agents and/or underlying disease (i.e., HIV).

This review did not identify any new safety issues with Dotarem in either pediatric or adult populations. However, since the data provided from FAERS is limited with respect to quantity of reports, the appropriate final labeling for Dotarem should be made based on all available data to the Review Division.

5 APPENDICES

[4] Camilli S, Gelperin K, et al. Acute Renal Failure and Gadolonium-based Contrast Agents, dated January 11, 2011.

5.1 APPENDIX A. PROPOSED DOTAREM LABELING REGARDING PREGNANCY AND LACTATION

Pregnancy **(Section 8.1 of label)**

Pregnancy Category C

There are no adequate and well-controlled studies conducted in pregnant women. DOTAREM Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DOTAREM Injection was not embryotoxic or teratogenic in rats and rabbits. A non-significant increase of incidence of incomplete or delayed ossification of some bones was observed in rats and rabbit fetuses born from female animals given daily dose levels starting from 4 mmol/kg/day in rats and 1 mmol/kg/day in rabbits from gestation day 6 to day 17 in rats or 19 in rabbits. These dose levels represented 6 and 3 times the human dose based on body surface area in rats and rabbits, respectively. Maternal toxicity was observed in rats at 10 mmol/kg/day (16 times the human dose based on body surface area) and in rabbits at 7 mmol/kg/day (23 times the human dose based on body surface area).

Nursing Mothers **(Section 8.3 of label)**

It is not known whether DOTAREM is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when DOTAREM is administered to a nursing woman.

NONCLINICAL DATA SHOW THAT DOTAREM IS EXCRETED INTO BREAST MILK IN VERY SMALL AMOUNTS (<0.1% OF THE DOSE INTRAVENOUSLY ADMINISTERED) AND THE ABSORPTION VIA THE GASTROINTESTINAL TRACT IS POOR.

5.2 APPENDIX B. PROPOSED DOTAREM LABEL WARNING AND PRECAUTION FOR NEPHROGENIC SYSTEMIC FIBROSIS, ADVERSE REACTIONS AND POSTMARKETING SECTIONS

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF) has occurred with other GBCAs exhibiting a low stability in patients with severe kidney disease. Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 – 59 mL/min/1.73m2) and little, if any, for patients with chronic, mild kidney disease (GFR 60 – 89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

Report any diagnosis of NSF following DOTAREM administration to Guerbet LLC (1-877-729-6679) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are the use of low stability GBCAs, repeated or higher than recommended doses of a GBCA, and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended DOTAREM dose and allow a sufficient period of time for elimination of the drug prior to re-administration. No unconfounded cases of NSF have been reported with DOTAREM. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown [*see Clinical Pharmacology (12) and Dosage and Administration (2)*].

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect DOTAREM exposure in 2813 patients, representing 2672 adults and 141 children. Most patients received doses between 0.05mmol/kg and 0.3mmol/kg body weight.

Overall, 54.6% of the patients were men. In clinical trials where ethnicity was recorded the distribution was 74% Caucasian, 12% Asian, 4% Black, and 10% others. The average age was 53 years (range from 0.1 to 97 years).

Overall, 3.9% of patients reported at least one adverse reaction, primarily occurring immediately or several days following DOTAREM administration. In total, 149 adverse reactions were reported. Most adverse reactions were mild or moderate in severity and transient in nature.

Table 2 lists adverse reactions that occurred in ≥0.2% patients who received DOTAREM.

Table 2: Adverse Reactions (≥0.2%)

Reaction	**Rate (%)** **n=2813**
Nausea	0.6%

Headache	0.5%
Injection Site Pain	0.4%
Injection Site Coldness	0.2%
Burning Sensation	0.2%

Adverse reactions that occurred with a frequency <0.2% in patients who received DOTAREM include: feeling cold, rash , somnolence, fatigue, dizziness, vomiting, pruritus, paresthesia, dysgeusia, pain in extremity, anxiety, hypertension, palpitations, oropharyngeal discomfort, blood creatinine increased, blood lactate dehydrogenase increased, injection site inflammation, injection site extravasation, injection site pruritus, injection site warmth, and asthenia.

Postmarketing Experience

To date, it is estimated that more than 30 million doses of Dotarem have been administered worldwide. The following adverse reactions have been identified during post approval use of DOTAREM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

System Organ Class	**Adverse Reaction**
Cardiac Disorders	bradycardia, tachycardia, arrhythmia
Immune System Disorders	hypersensitivity /anaphylactoid reactions including cardiac arrest, respiratory arrest, cyanosis pharyngeal edema, laryngospasm, bronchospasm, angioedema, conjunctivitis, ocular hyperemia, eyelid edema, lacrimation increased, hyperhidrosis, urticaria
Nervous System Disorders	coma, convulsion, syncope, presyncope, parosmia, tremor
Musculoskeletal and Connective Tissue Disorders	muscle contracture, muscle weakness
Gastrointestinal Disorders	diarrhea, salivary hypersecretion
General Disorders and Administration Site Conditions	malaise, fever
Skin and Subcutaneous Tissue Disorders	nephrogenic systemic fibrosis (Most often in patients who also have received other GBCAs. No unconfounded cases of NSF have been reported with DOTAREM.)
Vascular Disorders	superficial phlebitis

See Warnings and Precautions (5.1)

5.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

5.4 APPENDIX D. AERS CASE NUMBERS, AERS ISR NUMBERS AND MANUFACTURER CONTROL NUMBERS (N=51)

Pediatric Case Series (N=4)

AERS Case Numbers	ISR Numbers	Manufacturer Control Numbers
6553744	5614876	DE-GUERBET-20080005
6444840	5481015	FR-GUERBET-20070169
7246205	6538039	FR-ASTRAZENECA-2010SE00501
7332885	6660625,6652878	FR-ASTRAZENECA-2010SE12076

Adult Case Series (N=47)

AERS Case Numbers	ISR Numbers	Manufacturer Control Numbers
8319758	8019943	FR-ABBOTT-11P-056-0886841-00
6654816	5755369	DE-ROCHE-566325
5898297	4899318,4787083	BE 2005 0011
4177151	4397649	GB 2004 0006
6444878	5481023	JP-GUERBET-20070054
6662208	5755884	CH-GUERBET-20080007
4018614	4208098	FR 2003 0050
6322753	5343424,5331817	FR-GUERBET-20070100
4157783	4437546,4378666	DE 2004 0026
8090776	8209239,7684147	DE-BAYER-2011-067884
6553720	5614875	DE-GUERBET-20070085
7578060	7710170,7478352,6973396	DK-BAYER-201037560GPV
6289133	5694342,5473473,5485917,5442662,5398158,5298193,5318343	FR-BAYER-FR-2007-012919
6347665	5442580,5376508,5394576	DE-SHR-DE-2007-021759
6362525	5615810,5388687,5450968	CH-GUERBET-20070009
6391187	5425774	CH-SHR-CH-2007-025128
8887360		SG-PFIZER INC-2012272007
5830717	4713489,4698311	CH 2005 0007
8900191		DE-BAYER-2012-117405
7358426	6668575	FR-GUERBET-20100012
7904500	7423379	PHHY2011DE29422
6424421	5450969	CH-GUERBET-20070010
5972917	4899320,4887449	GB 2006 0001
8886304		JP-COVIDIEN/TYCO HEALTHCARE/MALLINCKRODT-T201203749
4177156	4342394	PHRM2004FR01509
7234806	6504126	OSCN-NO-0912S-0524
7602166	7008578	BE-WATSON-2010-12543
7806700	7268264	OMPQ-NO-1101S-0037
8109337	7713258	DK-BAYER-2011-047774
6069778	5024623	FR 2006 0064
6211448	5191926	FR-GUERBET-20060139
4105351	4312076	FR 2004 0009
4069250	4326234,4268874	BE 2003 0008

AERS Case Numbers	ISR Numbers	Manufacturer Control Numbers
6159810	5134060	DE-GUERBET-20060039
4122718	4326236	FR 2004 0008
4116593	4319091	FR 2004 0015
7073163	6292928	IT-GUERBET-20090014
7073165	6292909	FR-GUERBET-20080074
6322585	5330555	ES-GUERBET-20070002
7002789	6292914,6193593	IT-GUERBET-20090003
6049091	4996466	NL 2006 0002
6313390	5343423,5320924	FR-GUERBET-20070099
5972914	4887444	AR2005 0001
6352022	5375680	IT-GUERBET-20070021
6050831	5000020	FR 2006 0062
4176499	4399305	BE 2004 0001
6024875	4955832	FR 2006 0039

Appendix E. **Literature Citations Describing Safety of Gadoterate.**
Source: PubMed as of December 5, 2012.

	PMID	Article Citation	Comments
1	21786126	Emond S, Brunelle F. Gd-DOTA administration at MRI in children younger than 18 months of age: immediate adverse reactions. Pediatr Radiol. 2011 Nov;41(11):1401-6. Epub 2011 Jul 24.	See detailed description in Section 1.2.1. This post-marketing French study included 104 infants and neonates with an age range of 3 days to 18 months. No adverse events were noted.
2	21660638	Shah V, Shah S, Barnacle A, Sebire NJ, Brock P, Harper JI, McHugh K. Mediastinal involvement in lymphangiomatosis: a previously unreported MRI sign. Pediatr Radiol. 2011 Aug;41(8):985-92.	The emphasis of this article is using MRI/contrast to assess multifocal lymphangiomatosis. Retrospective review of 8 pediatric patients who received Dotarem. Ages ranged from 0.9 years to 10.7 years. Only 2 patients < 2 years included (0.9 years and 1.9 years). No specific adverse events mentioned.
3	21575211	Secinaro A, Ntsinjana H, Tann O, Schuler PK, Muthurangu V, Hughes M, Tsang V, Taylor AM. Cardiovascular magnetic resonance findings in repaired anomalous left coronary artery to pulmonary artery connection (ALCAPA). J Cardiovasc Magn Reson. 2011 May 16;13:27.	The emphasis of this article is using MRI/contrast to assess anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA). Retrospective review of 6 patients who received Dotarem. Ages ranged from 9.7 years to 21.7 years, therefore no patients < 2 years. No adverse events mentioned.
4	21279974	Galluzzi P, De Francesco S, Giacalone G, Cerase A, Monti L, Vallone IM, Lazzeretti L, Venturi C, Hadjistilianou T. Contrast-enhanced magnetic resonance imaging of fibrovascular tissue ingrowth within synthetic hydroxyapatite orbital implants in children. Eur J Ophthalmol. 2011 Sep-Oct;21(5):521-8.	The emphasis of this article is using MRI/contrast to assess implants inserted in anophthalmic sockets of children. Retrospective review of 23 patients who received Dotarem. The mean age at MRI examination was 56 months (age range, 9-145 months; median 53 months). 12 patients were < 2 years. No adverse events mentioned.
5	20052464	Merlini L, Combescure C, De Rosa V, Anooshiravani M, Hanquinet S. Diffusion-weighted imaging findings in Perthes disease with dynamic gadolinium-enhanced subtracted (DGS) MR correlation: a preliminary study. Pediatr Radiol. 2010 Mar;40(3):318-25. Epub 2010 Jan 6.	The emphasis of this article is using MRI/contrast to assess signal alteration imaging of bone in Legg-Calvé-Perthes disease. Review of 12 patients who received Dotarem. Ages ranged from 5 years to 12 years, therefore no patients < 2 years. No adverse events mentioned.
6	11960239	Mortelé KJ, Vanzieleghem B, Mortelé B, Benoit Y, Ros PR. Solitary hepatic infantile	The emphasis of this article is using MRI/contrast to assess hepatic infantile

		hemangioendothelioma: dynamic gadolinium-enhanced MR imaging findings. Eur Radiol. 2002 Apr;12(4):862-5. Epub 2001 Jul 25.	hemangioendothelioma in a 14 day-old girl. Dotarem was administered. No adverse events were reported.
7	11526287	Ruehm SG, Schroeder T, Debatin JF. Interstitial MR lymphography with gadoterate meglumine: initial experience in humans. Radiology. 2001 Sep;220(3):816-21.	Magnetic resonance lymphography was performed with gadoterate meglumine in five healthy volunteers and three patients (two adults and a 1 month-old infant). In the infant, a chylothorax was diagnosed. The authors concluded that interstitial magnetic resonance lymphography with commercially available compounds is feasible. No adverse events were mentioned.
8	11167332	Holmqvist C, Larsson E-M, Ståhlberg F, Laurin S. Contrast-enhanced thoracic 3D-MR angiography in infants and children. Acta Radiol. 2001 Jan;42(1):50-8.	The emphasis of this article is using MRI/contrast to assess suspected congenital heart or thoracic vessel malformation. Prospective study of 39 patients who received Dotarem. Ages ranged from 3 days to 15.5 years. 24 children were < 2 years. No adverse events mentioned.
9	9126573	Sebag G, Ducou Le Pointe H, Klein I, Maiza D, Mazda K, Bensahel H, Hassan M. Dynamic gadolinium-enhanced subtraction MR imaging–a simple technique for the early diagnosis of Legg-Calvé-Perthes disease: preliminary results. Pediatr Radiol. 1997 Mar;27(3):216-20.	The emphasis of this article is using MRI/contrast to assess ischemia of the femoral head in children with early Legg-Calve´ - Perthes disease. Review of 4 patients who received Dotarem. Ages ranged from 5 years to 9 years. Therefore, no children < 2 years included. No adverse events mentioned.
10	7596658	Borecky N, Gudinchet F, Laurini R, Duvoisin B, Hohlfeld J, Schnyder P. Imaging of cervico-thoracic lymphangiomas in children. Pediatr Radiol. 1995;25(2):127-30.	The emphasis of this article is using MRI/contrast to assess cervicothoracic lymphangiomas in children. Retrospective review of 11 patients who received Dotarem. Ages ranged from 1 month to 9 years and 2 months. 5 patients < 2 years included. No adverse events mentioned.
11	8078730	Bonnerot V, Sebag G, de Montalembert M, Wioland M, Glorion C, Girot R, Lallemand D. Gadolinium-DOTA enhanced MRI of painful osseous crises in children with sickle cell anemia. Pediatr Radiol. 1994;24(2):92-5.	The emphasis of this article is using MRI/contrast to assess osseous crises in sickle cell disease in children. Review of 9 patients who received Dotarem. Ages ranged from 6 months to 20 years. Mean age 11 years. Ages were not presented in tabular form, but at least 4 patients were older than age 2 years. No adverse events mentioned.

12	1727317	Hervé-Somma CM, Sebag GH, Prieur AM, Bonnerot V, Lallemand DP. Juvenile rheumatoid arthritis of the knee: MR evaluation with Gd-DOTA. Radiology. 1992 Jan;182(1):93-8.	The emphasis of this article is using MRI/contrast to assess synovial hypertrophy, effusion, and articular cartilage status. Review of 24 pediatric patients who received Dotarem. Mean age, 10 years, range, 3-18 years. Therefore no patients < 2 years included. No adverse events reported.
13	2092086	Romero C, Dietemann JL, Kurtz D, Bataillard M, Christmann D. Adrenoleukodystrophy. Value of contrast-enhanced MR imaging. J Neuroradiol. 1990;17(4):267-76.	Two boys aged 8 years and 9 years received MRI/contrast (Dotarem) to assess adrenoleukodystrophy. No patients < 2 years included. No adverse events reported.

5.5 APPENDIX F. SUMMARY OF SELECTED CASES (N=3) AND DESCRIPTIVE REVIEW OF ALL CASES CODED FOR NEPHROGENIC SYSTEMIC FIBROSIS (N=10)

The following case summaries are examples of the NSF cases reported for Dotarem. Case #6362525 and #7578060 are summarized to show examples of how the Dotarem NSF cases are confounded by administration of other GBCAs, and case # 8900191 is summarized to show that the case was not well documented and specifically did not document reduced renal function.

Case # 6362525. A 67-year-old female patient developed symptoms of NSF (sensation of finger and hand rigidity with feeling of hyperesthesia in her fingertips and sclerotic plagues, symmetric, with irregular borders, without pigmentation, situated around her leg joints) starting in 2005. She had a medical history of chronic renal failure since 1994 secondary to complications of diabetes mellitus and hypertension, and received peritoneal dialysis from 1995 until 18 March 1998 followed by hemodialysis. She received two angiograms with Dotarem (20mLs both instances) in 2004. In 2005, she received a magnetic resonance imaging scan of the spine with 20 mL of Dotarem for contrast and an angiogram of the lower extremities with 15 mL of Gadovist as a contrast agent (dosed approximately nine days prior to symptom onset). Her skin biopsy taken in April of 2006 was determined to support a diagnosis of NSF. Treatment with monthly extracorporal photopheresis was started. At the time of the report, the symptoms of NSF have not resolved. On follow-up, using the patients hospital records, she was found to have a total of seven procedures using a gadolinium agent (the four previously reported plus one using gadoteridol [in 2000], one using an unknown gadolinium agent [in 2000], and one an MRI of her knee in 1999 with 15ml gadopentetic acid [Magnevist; a linear gadolinium agent]).

Case # 7578060. A 61 year old male, with a history of renal disease secondary to hypertension, developed symptoms of NSF (itching skin, skin pain, pain in joint, edema in legs, skin changes, loss of sensation in fingers, and stiff legs) five months after his second (gadolinium administered in Jun 2002 and Sep 2002) administration of a gadolinium contrast agent (not specified). He started hemodialysis treatments mid-year during 2002 between the two gadolinium administrations. The patient did not receive Dotarem until October of 2006. He was diagnosed with NSF by the results of a skin biopsy in 2009. The NSF symptoms occurred prior to any administration of Dotarem.

Case # 8900191. A 39 year old male had three contrast enhanced computer tomographic studies using the gadolinium based contrast agents Magnevist (32 mLs dose; January 2011) once and Dotarem (18 mLs; first instance in April 2011) twice. Each administration of contrast agent was reported to be followed by a "high-dose" administration of an iodinated contrast agent (agent not reported). No measurement of the patient's kidney function was reported. The patient reported experienced nephrogenic systemic fibrosis (symptoms not reported) and polyneuropathy on February, 7, 2011. In December, the patient experienced an unspecified cardiac disorder. In January 2012, the patient experienced skin fibrosis. The patient reportedly received a skin biopsy; however, the results were not reported. On January 8, 2012, the patient's TGF-Beta was reportedly "highly increased" (value not reported). In this case, the reported onset of NSF was prior to the administration of Dotarem.

A descriptive listing of all 10 NSF cases follows:

Case Number	Patient Age (Years)	Patient Sex	Case Preferred Term(s)	Case Outcome(s)
8900191	39	MALE	NEPHROGENIC SYSTEMIC FIBROSIS, POLYNEUROPATHY, CARDIAC DISORDER, SKIN FIBROSIS	DISABILITY
8109337	45	MALE	NEPHROGENIC SYSTEMIC FIBROSIS, MUSCULAR WEAKNESS, OEDEMA PERIPHERAL, PRURITUS, WALKING DISTANCE TEST ABNORMAL, MUSCULOSKELETAL STIFFNESS, DIPLEGIA,HYPOAESTHESIA, MUSCLE SPASMS, GENERAL PHYSICAL HEALTH DETERIORATION, PAIN IN EXTREMITY, INSOMNIA,RESTLESS LEGS SYNDROME, SKIN INDURATION, ANXIETY, POLYNEUROPATHY, LIMB INJURY	DISABILITY, OTHER OUTCOMES
7234806	46	MALE	LEG AMPUTATION, POOR PERIPHERAL CIRCULATION, NEPHROGENIC SYSTEMIC FIBROSIS	OTHER OUTCOMES
6424421	49	MALE	NEPHROGENIC SYSTEMIC FIBROSIS, DECUBITUS ULCER, EPILEPSY, DRUG WITHDRAWAL SYNDROME, SOMNOLENCE, DISORIENTATION, SEPSIS, INTERVERTEBRAL DISCITIS, GENERAL PHYSICAL HEALTH DETERIORATION, FEMUR FRACTURE, FOOT AMPUTATION, GROIN ABSCESS, TRANSIENT ISCHAEMIC ATTACK, CATARACT, LOBAR PNEUMONIA, STAPHYLOCOCCAL INFECTION,LOCALISED INFECTION, TOE AMPUTATION	DEATH, DISABILITY, REQUIRED INTERVENTION
6347665	49	MALE	NEPHROGENIC SYSTEMIC FIBROSIS	DISABILITY
7602166	55	MALE	NEPHROGENIC SYSTEMIC FIBROSIS,COLITIS MICROSCOPIC	OTHER OUTCOMES
6362525	67	FEMALE	NEPHROGENIC SYSTEMIC FIBROSIS, TOXICITY TO VARIOUS AGENTS	DISABILITY, REQUIRED INTERVENTION
6391187		FEMALE	NEPHROGENIC SYSTEMIC FIBROSIS	HOSPITALIZATION
6289133	60	FEMALE	NEPHROGENIC SYSTEMIC FIBROSIS	DISABILITY, HOSPITALIZATION
7578060	61	MALE	NEPHROGENIC SYSTEMIC FIBROSIS, PRURITUS, PAIN OF SKIN, ARTHRALGIA, OEDEMA PERIPHERAL, JOINT RANGE OF MOTION DECREASED,APPETITE DISORDER, ASTHENIA, FATIGUE, SKIN DISORDER, HYPOAESTHESIA, MOTOR DYSFUNCTION, RESTLESS LEGS SYNDROME, GAIT DISTURBANCE, MUSCULOSKELETAL STIFFNESS, SKIN DISCOLOURATION, MOBILITY DECREASED, PAIN, SKIN INDURATION	DISABILITY

5.6 APPENDIX G. SUMMARY OF SELECTED CASES (N=5) AND DESCRIPTIVE LISTING OF THE CASES GROUPED AS HYPERSENSITIVITY REACTIONS (N=22)

The following case summaries are examples of hypersensitivity reaction cases reported for Dotarem:

Case # 4105351. A 33 year old non-atopic female lost consciousness and had generalized erythema immediately after injection of 100 mL of Dotarem for a cranial MRI. She recovered from the reaction after administration of epinephrine and restoration of her blood volume with intravenous fluids. Her hypersensitivity to gadoterate was proven by the positive results of an intradermal test and an in vitro leukocyte histamine release test.

Case # 5972914. A 36 year old female was administered 10 mLs of Dotarem for a non-reported indication, and immediately experienced throat discomfort, breathing difficulties, edema of the glottis, sphincter incontinence, hypotension, a reduced pulse rate, and generalized edema. The patient was administered oxygen, hydrocortisone, intravenous saline and transferred to the intensive care unit. She was treated for two days in the intensive care unit and recovered from all events.

The following case summaries are of possible immunologic/hypersensitivity reactions with skin involvement and one case of erythema multiforme associated with Dotarem use:

Case # 8090776. A 71 year old male received multiple administrations (doses not reported) of gadolinium contrast agents (Dotarem [March 2009 and December 2010], Multihance [December 2009], and Gadovist [March and December 2010]) for post therapy evaluation by magnetic resonance imaging of a retromolar squamous cell carcinoma over a two year period of time. He developed blackish brownish skin blemishes of about 3-5 centimeters a few days after each administration. The blemishes did not resolve and increased in intensity with each subsequent gadolinium contrast administration. He also experienced hyperpigmentation of his skin over his whole body which did not resolve. The symptoms were reported as, "circular skin hyperpigmentation all over the body." No evaluation of the patient's renal function was reported. The case stated, "lab data (retention values) all in normal range." He received no treatment for the disorder. He underwent dermatologic examinations in 2010 and 2011 with histologic evaluation. NSF was not diagnosed. The histology results from a skin biopsy of the right upper arm was reported as, "postinflammatory pigment incontinence; no findings of sclerosis." Histologic evaluation of a skin biopsy taken from his lower leg was reported as, "lichenoid inflammatory reaction with findings of neutophiles granulocytes in inflammatory infiltration in stratum papillare. Findings of marked pigment incontinence explained the impression of grayish pigmentation." The dermatologist findings of the histologic exams were reported as an immune reaction or a drug reaction. No definitive diagnosis of the patient's symptoms was reported.

Case # 6322753. A 48 year old female, with history of human immunodeficiency virus infection and chronic renal failure treated with dialysis, received 15 mLs of Dotarem for an MRI of the rachis to explore lumbar and neuropathic pain from a spinal fracture. The next day she experienced a skin eruption on the arms (8 centimeter area on the left forearm), hands, and in the lumbar region. The affected area on the left forearm was surrounded by an infiltration

resembling the skin of an orange peel. Her skin was biopsied and the histologic evaluation of the tissues provided the following diagnoses: "excoriee lesions of which the histological examination did not find any specific character, nor calciphylaxia, nor toxiderma." The hospital report said, "an immunoallergic origin cannot be ruled out, but the diagnosis cannot be confirmed." Her lumbar area was treated with first a steroid cream and then electrical stimulation without effect. She was administered Lyrica, which did not help the pain in her lumbar area. She then was treated with Rivotril. The outcome for the reactions was not recovered.

Case # 8886304. A 68 year old female received Dotarem (dose not reported) for MRI evaluation of breast cancer and, a day later, 100 mLs of Optiray for a computer tomographic (CT) study to evaluate her breast cancer. Six days after the Dotarem administration, she reported to the emergency room with a rash. She was treated with chlorpheniramine maleate drip intravenously and olopatadine hydrochloride orally. The erythema spread to her entire body. She was admitted to the hospital and diagnosed with erythema mutiforme exudativum. She was placed on multiple medications and recovered without sequelae after 13 days (9 days in hospital).

Reviewers Comment: *This case is confounded by the concomitant administration of Optiray.*

A descriptive listing of all 22 cases described as hypersensitivity reactions follows:

Case Number	Patient Age (Years)	Patient Sex	Case Preferred Term(s)	Case Outcome(s)
6069778	NOT REPORTED	MALE	URTICARIA, CARDIOGENIC SHOCK	HOSPITALIZATION, LIFE THREATENING
4105351	33	FEMALE	ANAPHYLACTIC SHOCK, LOSS OF CONSCIOUSNESS, CONVULSION, GENERALISED ERYTHEMA, DRUG HYPERSENSITIVITY, HYPOTENSION	HOSPITALIZATION, OTHER OUTCOMES
5972914	36	FEMALE	DYSPNOEA, THROAT TIGHTNESS, HYPOTENSION,HEART RATE DECREASED, LARYNGEAL OEDEMA, GENERALISED ERYTHEMA, FAECAL INCONTINENCE, URINARY INCONTINENCE	HOSPITALIZATION, LIFE THREATENING
7073163	42	FEMALE	URTICARIA, PRURITUS, EYELID OEDEMA, CYANOSIS, STRIDOR, LARYNGEAL OEDEMA, DYSPNOEA, NASAL CONGESTION	HOSPITALIZATION
7073165	42	FEMALE	ANAPHYLACTOID REACTION, VERTIGO,MALAISE, HYPOTENSION, HYPERHIDROSIS, PALLOR,ERYTHEMA, RASH PAPULAR	HOSPITALIZATION, REQUIRED INTERVENTION
7358426	42	FEMALE	DRUG HYPERSENSITIVITY, ANGIOEDEMA, DYSPHONIA, DYSPHAGIA, BLOOD PRESSURE SYSTOLIC INCREASED, HEART RATE INCREASED, BODY TEMPERATURE INCREASED	HOSPITALIZATION
4069250	44	FEMALE	RASH, DYSPNOEA, TACHYCARDIA, URTICARIA, PERIORBITAL OEDEMA, EYE OEDEMA, CONJUNCTIVAL OEDEMA	HOSPITALIZATION

Case Number	Patient Age (Years)	Patient Sex	Case Preferred Term(s)	Case Outcome(s)
6159810	47	FEMALE	HYPOTONIA, RASH, ERYTHEMA,URTICARIA, PRURITUS,PROCEDURAL COMPLICATION	HOSPITALIZATION, REQUIRED INTERVENTION
4177151	49	MALE	THROAT TIGHTNESS, URTICARIA, THROAT IRRITATION	HOSPITALIZATION
6322585	51	FEMALE	RESPIRATORY FAILURE,THROAT IRRITATION	HOSPITALIZATION, REQUIRED INTERVENTION
6050831	53	MALE	MALAISE, HYPOTENSION, URTICARIA, PHARYNGEAL OEDEMA, EPISTAXIS	HOSPITALIZATION, LIFE THREATENING
4116593	59	FEMALE	HYPOTENSION, BRONCHOSPASM, FACE OEDEMA, OEDEMA PERIPHERAL, ERYTHEMA	HOSPITALIZATION, LIFE THREATENING
6654816	62.9	FEMALE	RHABDOMYOLYSIS, DRUG HYPERSENSITIVITY, AMAUROSIS FUGAX, VENTRICULAR TACHYCARDIA, ASYMPTOMATIC BACTERIURIA, HYPOKALAEMIA	HOSPITALIZATION, OTHER OUTCOMES
7002789	65	MALE	PRURITUS, URTICARIA	HOSPITALIZATION
6313390	65	MALE	COMA, CARDIAC ARREST, CLONIC CONVULSION, VOMITING, LOSS OF CONSCIOUSNESS, RESPIRATORY DISTRESS, CONTRAST MEDIA REACTION	HOSPITALIZATION, LIFE THREATENING, REQUIRED INTERVENTION
4157783	65	MALE	MYOCARDIAL INFARCTION, ANAPHYLACTIC SHOCK, PALLOR, CONVULSION,HEART RATE DECREASED, VENTRICULAR FIBRILLATION, HYPERHIDROSIS, DYSPNOEA,CARDIOVASCULAR DISORDER, CONTUSION,SKIN DISCOLOURATION,INCREASED VENTRICULAR PRELOAD, ATRIAL FIBRILLATION, LUNG DISORDER, VENTRICULAR DYSKINESIA, ERUCTATION, NAUSEA, RESPIRATORY DISORDER,INJURY, ACUTE CORONARY SYNDROME	HOSPITALIZATION, LIFE THREATENING
8886304	68	FEMALE	ERYTHEMA MULTIFORME	HOSPITALIZATION
8090776	71	MALE	SKIN HYPERPIGMENTATION	DISABILITY, HOSPITALIZATION, OTHER OUTCOMES
4176499	74	MALE	ANAPHYLACTIC SHOCK, HYPOTENSION,DIZZINESS, CHEST PAIN, LOSS OF CONSCIOUSNESS, ERYTHEMA	HOSPITALIZATION, LIFE THREATENING, OTHER OUTCOMES
5898297	78	FEMALE	INFLAMMATION, PYREXIA,SKIN REACTION, PRURITUS, RASH PAPULAR, URTICARIA, HEADACHE, RASH ERYTHEMATOUS	HOSPITALIZATION
8887360	NOT REPORTED	FEMALE	RASH	HOSPITALIZATION, OTHER OUTCOMES
6322756	48	FEMALE	DERMATITIS, BACK PAIN, BONE PAIN, CARDIOMEGALY, HAEMOGLOBIN	HOSPITALIZATION

Case Number	Patient Age (Years)	Patient Sex	Case Preferred Term(s)	Case Outcome(s)
			DEREASED, DERMATITIS, SKIN ULCER, ABDOMINAL PAIN, RETICULOCYTE COUNT ABNORMAL, TRANSFERRIN DECREASED, SERUM FERRITIN INCREASED, C-REACTIVE PROTEIN INCREASED, HEPATITIS B SURFACE ANTIBODY	

5.7 APPENDIX H. CASE SUMMARIES FOR REMAINING LABELED EVENTS OCCURRING IN ADULTS (N=6)

Coma, Pulmonary Edema (n=1)

Case # 4122718. A 59 year old female, with a history of unstable arterial hypertension following previous MRIs, received an unreported dose of Dotarem for an unreported indication. She reported feeling strange, and, reportedly, fell into a "coma" at an unreported time after the administration. She was hospitalized and found to have developed pulmonary edema. On follow-up, the physician attributed the pulmonary edema to her underlying "long-standing" and "neglected" cardiac disease.

Convulsions (n=1)

Case # 5972917. A 31 year old male, with past history of epilepsy, received an intravenous injection of 1 mL of Dotarem for an unreported indication. As the injection began, he experienced an epileptic seizure with loss of consciousness. The injection was stopped, the "crash team" was called, and he was transferred to the intensive care unit for observation. He recovered from the event on the same day.

Dizziness (n=1)

Case # 6352022. A 41 year old male was administered Dotarem for an unreported indication at an unreported dose. At an unspecified time after the injection, he experienced dizziness and dryness in the back of his throat. The injection was stopped and he was administered oxygen though a face mask and an intravenous infusion of sodium chloride solution. The final outcome of the event was not reported.

Fever, Chills (n=1)

Case # 5830717. A 23 year old female received 2 mLs of Dotarem and 1 mL of iopamidol intraarticularly for a magnetic resonance arthrography of her wrist. She experienced fever and shivering about six hours after the injection that lasted for 24 hours. The patient recovered completely from the reaction.

Loss of Consciousness (n=2)

Case # 6444878. A 77 year old male, with past medical history of bouts of temporary loss of consciousness, received an MRI with 10 mLs of Dotarem, and, just after the injection, suffered from loss of consciousness and respiratory arrest. He was administered oxygen, SoluCortef and

dexchropheniramine maleate, and endotracheal intubation was attempted. The patient began to breath adequately on his own prior to endotracheal tube insertion; the insertion was stopped. He recovered the same day. No swelling of his throat was noticed on examination during the intubation procedure.

Case # 6049091. A 41 year old male, with past history of convulsion and internal carotid artery dissection after a previous MRI, was administered 25 mL of Dotarem for magnetic resonance angiography to further evaluate his Horner's Syndrome. Two minutes after the injection, he experienced a loss of consciousness, cardiac failure, and foaming at his mouth. He was also expected to have experience a seizure. The patient was started on cardiopulmonary resuscitation and administered 2 mg Tavegil, epinephrine, and prednisone (doses not reported). The patient recovered.

5.8 APPENDIX I. CASE SUMMARIES FOR UNEXPECTED ADVERSE EVENTS PER DOTAREM'S PROPOSED LABELING (N=9)

Acute Renal Failure (n=3;unexpected; blood creatinine increase listed in proposed label; Other *GBCAs in class are labeled for acute kidney injury [class labeling recommended by prior OSE review]*)

Case # 6553720. A 78 year old male, with a history of chronic renal failure (initial serum creatinine 2.15 mg/dL), diabetes mellitus, and hypertension, received an unreported amount of Dotarem for an evaluation of coronary artery disease/ischemia. He was admitted to the intensive care unit nine days after the administration with acute renal failure. About one week prior to this admission, he started to feel week, experienced a loss of appetite, and experienced apathy. On admission, his serum creatinine was 12.91 mg/dL and serum urea was 315 mg/dL. All non-critical medications were stopped, and he received a session of hemofiltration followed by intermittent hemodialysis for 10 days (3 times). His renal function recovered. His serum creatinine and blood urea nitrogen at discharge were 1.18 and 52 mg/dL, respectively. Although the patient was receiving multiple chronic medications, the reporting physician attributed the acute renal failure to Dotarem, since it was administrated shortly prior to the onset of the acute renal failure symptoms.

Case # 6024875. A 78 year old female, with a history of diabetes mellitus, bypass surgery, and a removed sigmoid tumor, received "40 mg" of Dotarem for an unknown indication. At an unreported time after the injection, she developed acute renal failure with a peak serum creatinine of 60 mg/dL. It was reported that she recovered from the reaction.

Case # 7806700. An 18 year old female, with a history of glioblastoma treated with Temodar and local radiation treatments, developed symptoms of bilateral renal colic on September 15, October 6, and October 21, 2010. In August 2010, prior to the symptoms of renal colic, she received two administrations of Dotarem (listed in the case as a suspect medication). Other medications listed in the case as suspect medication for the renal events described were Temodar, Omnipaque, esomeprazole, and pentamidine.

Acute Cholestatic Hepatitis and Acute Renal Failure (n=1; unexpected)

Case # 7904500. A 60 year old female, with a history of surgery for stenosis of the lumbar spinal canal, experienced cholestatic hepatitis with an increase in serum creatinine (value not specified; event started 17 days after Dotarem administration). Several suspect medications were started between 15 and 17 days prior to the event's onset. The other suspect products included voltaren, flucloxacillin, diclofenac, and clindamycin. Her alanine aminotransferase level went from 20 U/I (the day prior to the event) to 305 U/I. Her aspartate aminotransferase was increased at 139 U/I, and her bilirubin level increase to 3.01 mg/dL from 0.43 mg/dL. Her serum creatinine was also elevated (value unreported). All drugs listed above were discontinued and all the laboratory values listed above returned to normal levels 21 days after the event's onset (alanine aminotransferase level of 21 U/I; aspartate aminotresferase level of 19 U/I; bilirubin level 0.56 mg/dL). The reporter stated that narrowing the cause of the hepatic and renal adverse events to one agent would be difficult, since the agents were all started and stopped around the same time.

Reviewer Comment: *Dotarem most likely was not the causative agent since its administration was 17 days prior to the onset of the adverse events in question and the adverse events abated soon after the other agents were stopped.*

Thrombosis (n=2; unexpected; superficial phlebitis listed in proposed label)

Case # 6662208. A 47 year old male, with past history of a pulmonary embolism, underwent magnetic resonance imaging (MRI) with Dotarem (dose not reported) as contrast to evaluate a possible bone fracture. The day after the Dotarem administration, he complained of pain in his arm. The area was cooled and diclofenac ointment was administered as treatment. A doppler sonograph of his arm revealed a partial thrombosis of the vena cephalica in the right arm. He recovered from the symptoms in about seven weeks. The reporting physician classified the causal relationship between Dotarem and the adverse event as probable.

Case # 4177156. A male of unknown age, with a past history of epilepsy treated with Tegretol and surgical removal of a meningioma, received an injection of Dotarem and Magnevist for an MRI to evaluate his status post menigioma surgery. A few hours after the exam, he experienced severe frontal cephalgia. Three days later, he presented with flaccid paraparesis of the left arm which evolved into complete left-sided paralysis. His temperature was elevated to 38 degrees Celcius. Cardiac and pulmonary examinations did not reveal any abnormalities. His plasma CRP was 35 mg/L and his D-dimer was increased. An MRI the next day showed a hypersignal of the upper longitudinal sinus which was diagnosed as thrombophlebitis of the upper longitudinal sinus (this finding was not present on the previous MRI). He was treated with heparin and made a complete recovery from all symptoms.

Agranulocytosis (n=1; unexpected)

Case # 8319758. A 44 year old male, with a history of human immunodeficiency virus infection, was treated for a suspected atypical mycobacterium infection with ethambutol and clarithromycin. A day after therapy initiation, he developed agranulocytosis (white blood cells

count from 7100 to 700/mm^3) and pancytopenia (hemoglobin measurement from 9.6 to 7.3 mg/dL; platelet count from 124,000/mm^3 to 43,000/mm^3). He had also received Dotarem at an unspecified dose for an MRI for an unspecified indication five days prior to the onset of the pancytopenia. Therapy with ethambutol and clarithromycin was discontinued, and he was transfused with packed red blood cells. After the drugs were discontinued and the packed red blood cell transfusion completed, his pancytopenia slowly improved and the patient recovered.

Intrathecal Administration/Medication Error (n=1; unexpected)

Case # 4018614. A 67 year old man, with a history of normal pressure hydrocephalus, underwent cerebral MRI with 15 mLs of Dotarem; however, the Dotarem was injected intrathecally instead of through a venous line. He subsequently developed malaise, convulsions (three episodes of status epilepticus), bradycardia, ventricular tachycardia, hallucinations, vomiting, and a confusional state. He was transferred to the Neurosurgical unit and maximal drainage of cerebrospinal fluid was performed to remove the contrast agent. The patient was started on an anticonvulsant (rivotril, clonazepam, and phosphenytoin) and his confusion and convulsions improved; however, he was unable to walk (he could walk with difficulty prior to the incident). On follow-up, he is reported to be able to walk, but ataxia persists. He, otherwise, has recovered from the incident.

Vagal Reaction (n=1; unexpected; bradycardia labeled in proposed postmarketing section)

Case # 6211488. A female (age not reported) received Dotarem for an MRI and experienced vagal malaise. Her heart rhythm was recorded during the MRI by electrocardiogram (ECG). At an unreported time after Dotarem administration, the ECG recorded heart rhythm stopped for a few seconds and then restarted. The MRI was stopped. She experienced nausea and malaise after the heart rhythm recording restarted. The final outcomes for the adverse events were not reported.

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/s/

MICHAEL E KIEFFER
01/08/2013

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01/08/2013

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01/08/2013

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	204-781	**Brand Name**	Dotarem (Meglumine gadoterate) Injection
OCP Division V	V	**Generic Name**	N/A
Medical Division	Division of Medical Imaging Products	**Drug Class**	Gd based contrast agent
OCP Reviewer	Christy S. John, Ph.D.	**Indication(s)**	DOTAREM is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and **pediatric patients (from neonates to 17 years of age)** to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
OCP Team Leader	Gene Williams, Ph.D.	**Dosage Form**	Clear Solution
		Dosing Regimen	0.1 mmol/kg
Date of Submission	09/20/2012	**Route of Administration**	Intravenous Injection
Estimated Due Date of OCP Review	01/20/2013	**Sponsor**	Guerbet, LLC.
PDUFA Due Date	03/20/2013	**Priority Classification**	1P
Division Due Date	02/20/2013		

Clin. Pharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary	**X**			
Labeling				

Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology	**X**			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:				
Patients-				
single dose:	X			
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				

alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**	**1**		
Total Number of Studies	**X**	**4**		

Filability and QBR comments

	"X" if yes	**Comments**
Application fileable ?	**X**	Dotarem proposed in this NDA has been approved in Europe since 1989 and many other countries and its formulation is identical to the one used in all pre-clinical and clinical trials supporting this NDA. There are no filing issues.
Comments sent to firm ?	None	
QBR questions (key issues to be considered)	There is no dose finding study. The sponsor has chosen dose based on magnevist (approved Gd agent). Is it reasonable? There is no collection of blood for PK in pediatric population, yet the sponsor is seeking pediatric age group indication. Is it adequate and justified based on clinical efficacy data?	
Other comments or information not included above		
Primary reviewer signature	**Christy S. John, Ph.D.**	
Secondary reviewer Signature and date	**Gene Williams, Ph.D.**	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
11/14/2012

GENE M WILLIAMS
11/14/2012