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

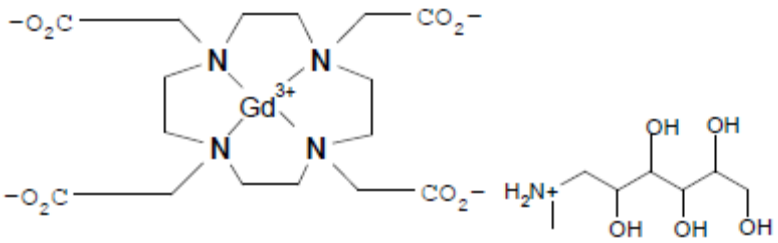
2.2. General Attributes of the Drug

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)

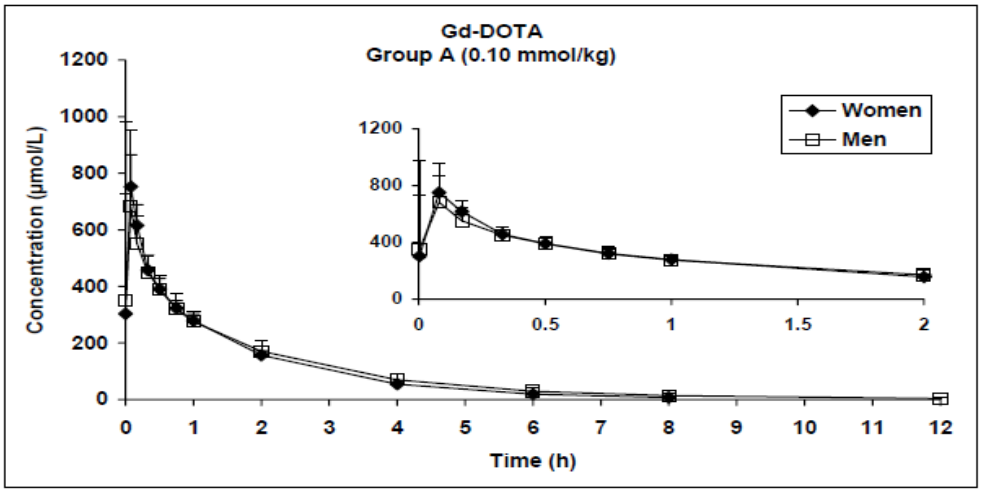


Figure 2. Mean and SD plasma concentration versus time profiles of Gd-DOTA – Group B (0.10 + 0.2 mmol/kg)

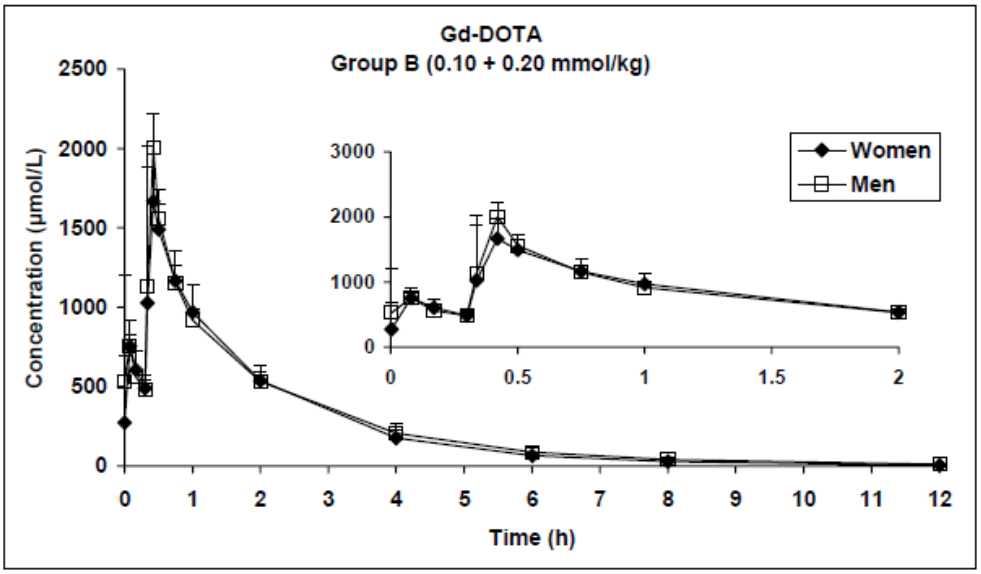


Table 4. Pharmacokinetic properties of Dotarem after injection of 0.1 mmol/kg

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

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