

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204781Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	February 19, 2013
<b>From</b>	Alex Gorovets, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA#</b>	204781
<b>Applicant</b>	Guerbet LLC
<b>Date of Submission</b>	September 20, 2012
<b>PDUFA Goal Date</b>	March 20, 2013
	Priority Review
<b>Proprietary Name / Established (USAN) names</b>	Dotarem / Gadoterate Meglumine
<b>Dosage forms / Strength</b>	Single dose 0.1 mmol/kg of 0.5 mmol/ml intravenously
<b>Proposed Indication(s)</b>	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 neonate to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
<b>Recommended:</b>	<i>Approval in adults and children two years of age and older</i>

### 1. Introduction

The subject of this document is the Cross-Disciplinary Team Leader (CDTL) review of the New Drug Application (NDA) # 204781 for the use of Dotarem with magnetic resonance imaging (MRI) of the central nervous system (CNS) in adults and pediatric patients (from neonate to 17 years of age).

Dotarem, or Gadoterate Meglumine, is a Gadolinium Based Contrast Agent (GBCA) and is one of many in the class of such agents approved in this country for similar use in adults and children over two years of age. What distinguishes this application from others is the applicant's claim for use of their product is neonates and infants, i.e. children 0 through 23 months of age, or up to the age of two years old. Given that such a claim addresses an unmet medical need the application has been given a designation of Priority review.

The applicant's claim of Dotarem safety and effectiveness relies on the results of two multi-center confirmatory Phase-3 trials, three single center pediatric observational studies and multiple other supportive non-US post-marketing studies and publications. Whether these data represent sufficient evidence for approval of this drug in pediatric patients, especially in those less than two years of age, constitutes the main review issue associated with this application. No major disagreements among disciplines have been encountered during the review process.

## 2. Background

GBCAs are an important class of diagnostic drugs commonly used with MRI for evaluation of CNS tumors as well as other CNS pathology. These drugs accumulate in the areas associated with the Blood Brain Barrier disruption and abnormalities of CNS vasculature. As they increase the proton relaxivity in the area of extra-vascular accumulation they provide the necessary contrast for an improved visualization. Demonstrating improved lesion visualization using contrast, or contrast plus non-contrast (paired), images compared to non-contrast images, according to pre-specified visualization categories, has served as the regulatory pathway to approval of GBCAs in this country. The first GBCA, Magnevist, was approved in 1988, and currently eight GBCAs are approved in US, six of these for a CNS indication, and five of these for adults and pediatric patients older than two.

The main risks associated with use of GBCAs are the recently described Nephrogenic Systemic Fibrosis (NSF), hypersensitivity reactions including anaphylaxis and an acute kidney injury usually in a setting of pre-existing renal insufficiency. NSF is a seriously disabling condition directly associated with gadolinium toxicity in patients with chronic renal failure or acute kidney injury. Based on the number of postmarketing reports of NSF and other considerations, the GBCAs as a class have been divided into high risk and low risk agents, with all agents carrying a black box warning and the high risk agents being in addition contraindicated in renally impaired patients. Of the currently approved GBCAs for a CNS indication, Magnevist, Omniscan and Optimark, the latter not specifically approved in children of any age, are in the high risk group; Prohance, Multihance and Gadavist are in the low risk group.

From the pediatric drug development standpoint, pediatric population has been subdivided in this country into four age groups: twelve through sixteen, six up to twelve, two to six and less than two (infants and neonates). Although, so far, no NSF cases have been reported in patients less than 8 year of age, there has been a special concern about using these drugs in patients less than two years of age because of kidney immaturity and consequently reduced Glomerular Filtration Rate (GFR) as compared to older children and adults, especially in children less than 12 months of age. Therefore development of GBCAs in pediatric population has required special consideration.

Currently, pediatric drug development in this country is being conducted according to the two sets of regulations: Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA), the latter mostly dealing with issues of pediatric exclusivity. With the clinical indications for use of GBCAs in children, including those under two, being in general similar to those in adults, PREA is the set of regulation applicable, at the present time, to the development of these drugs for use in children.

An important concept communicated in PREA is that, if diseases and drug effects are similar in adults and pediatric patients, "pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetics studies". Therefore separate safety and efficacy studies do not necessarily have to be conducted in pediatric patients in every case. However,

also according to PREA, unless waived or deferred, pediatric development has to involve all pediatric age groups. Although the formulation of the concept of extrapolation of adult data does not specifically address safety it has been understood that a supplemental study providing dosing information in pediatric patients could also serve as an exploratory study of safety.

In relation to the GBCAs marketed in US for the CNS indication in pediatric patients, the three “older” pre-PREA drugs, Magnevist, Prohance and Omniscan, refer in their respective labeling to safety and efficacy information obtained in Phase-3 clinical trials leading to the approval of their use in patients two years of age and older. A more recently approved Multihance was studied according to the specific post-marketing commitments addressing safety and efficacy in pediatric patients two years of age and older and also providing pharmacokinetic (pK) information. Due to the heightened concern over NSF at the time, the studies of Multihance in neonates and infants were waived under PREA.

The most recently approved GBCA was Gadavist marketed in US in 2011. In that application, the confirmatory Phase-3 trials did not contain pediatric data but the applicant provided pK and safety data obtained in over 100 pediatric patients aged two years and older. These data were similar to those in adults and Gadavist was approved at the same dose for use in both adults and pediatric patients aged two years or older. The approval was accompanied by a post-marketing requirement under PREA to evaluate the use of Gadavist in infants and neonates by first conducting a non-clinical study in juvenile animals and, if no safety signals were found, following it by a clinical pK and safety study in about 40 children representing this patient population. The non-clinical study has been completed and the clinical study is ongoing.

Of note, all GBCAs for the CNS indication are approved for use with the same dosing recommendation of 1 mmol/kg for children over two and for adults. A further consideration of the pediatric indication is provided below in Section 10: Pediatrics. The issue was also the subject of discussion at the recent Advisory Committee meeting (see Section 9).

Dotarem has been approved throughout Europe (first in France in 1989) and in many countries around the world. In most but not all, it is approved without age restrictions. Although it is estimated to have been used in over 30 million patients, no un-confounded cases of NSF have been reported with the use of Dotarem in either adults or in children. It is considered to be the most chemically stable of all GBCAs by being both macrocyclic and ionic.

Presently, in this country, GBCAs are used “off-label” when the use of contrast is required for MRI exams of the CNS in infants and neonates. Recognizing the public health value of establishing evidence of safety and effectiveness of a GBCA in this patient population FDA encouraged the applicant, when queried at the pre-NDA meeting, to provide the available data on the use of Dotarem in patients of all ages in the current NDA. Development of Dotarem for marketing approval in this country has taken place under the Investigational New Drug (IND) application # 65410.

### **3. CMC/Device**

Although the primary CMC review has not been finalized at the time of the completion of the CDTL review, the CMC reviewer appears to be in agreement with the applicant that Dotarem, or gadoterate meglumine, is a paramagnetic macrocyclic ionic agent. It is a stable compound with high thermodynamic and kinetic stability constants. The clinical relevance of such stability found in vitro is unclear. The important chemical parameters will be listed in the labeling.

Results of the facilities' inspections are pending.

CDRH has been consulted on the use of a syringe for Dotarem administration and device recommendations will be reflected in the labeling.

## 4. Nonclinical Pharmacology/Toxicology

The review of submitted data has not revealed any major concerns about safety of Dotarem when used in adults and older children. No juvenile animal data have been submitted. The reviewer is unable to recommend approving Dotarem in children less than two years of age.

## 5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review has confirmed that the proposed dose of Dotarem 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).

There are four clinical pharmacology studies submitted to the NDA. The studies in healthy volunteers provided information including descriptive pharmacokinetic, urinary excretion, and the effects of repeat acute dosing. The pK were linear. The QT study showed that Dotarem has no effect on QTc. A specific population pK study conducted in subjects with renal impairment has shown that renal elimination decreases as renal impairment increases. The AUC is nine-fold higher in patients with severe renal impairment. With imaging being conducted shortly after drug administration and before much clearance can occur, the review team does not recommend reducing dose to adjust AUC to that occurring in non-impaired subjects as it could compromise the imaging drug's performance.

Here are some pharmacology parameters, listed in Clinical Pharmacology review: Dotarem, like other gadolinium contrast agents, has a relatively short elimination half-life ( $1.32 \pm 0.24$  hours). Dotarem volume of distribution approximates extracellular space (about 16 L in males). In vitro plasma protein binding is less than 4%. After a single intravenous injection of 0.1 mmol/kg dose of Dotarem to healthy subjects,  $86.6 \pm 10.3$  % of the gadolinium is recovered in urine over 48 hours.

Because of the immature kidneys in younger children and with no pharmacokinetic data to establish the optimal dose for those less than two, the clinical pharmacology reviewer recommends a post-marketing requirement to obtain such data.

## **6. Clinical Microbiology**

This is not an antimicrobial therapeutic.

## **7. Clinical/Statistical- Efficacy**

The applicant has based the efficacy conclusions on the results of two confirmatory Phase-3 trials, -050 and 051. The -050 trial was conducted under a Special Protocol Assessment (SPA) at multiple international sites including the US. The study design, analyses and safety monitoring were agreed upon with the FDA. The -051 trial was a reread of the previously failed Phase-3 trial conducted earlier outside US. Although the -051 trial was conducted with the new efficacy endpoints, similar to the ones used in the -050 trial and also agreed to by the FDA, the reviewers regard the -050 as the main confirmatory trial and the -051 as the main supportive trial. In addition to these two trials the applicant has submitted the results from an extensive list of other clinical trials, Phase 2, 3, and 4, conducted outside US. This review mainly touches upon adult data in the trial -050, with a lesser emphasis on -051. Pediatric data originating from sources other than -050 are discussed below in Section 10.

The -050 trial was an adequate and well-controlled, multi-center, international Phase III clinical trial. Patients were enrolled in the trial after being referred for the contrast MRI of the central nervous system and were randomized 2 to 1 to receive either Dotarem or gadopentetate at a dose of 1mmol/kg. Patients first underwent a baseline (pre-contrast) MRI examination followed by a post-contrast examination. The images (pre-contrast, post-contrast and paired pre- and post-) were interpreted by three independent off-site readers who were blinded to clinical information. The primary efficacy endpoint was pre-specified to be assessed in adults only and was pre-specified to be a patient level superiority of Dotarem MRI (paired images) over baseline MRI (pre-contrast images) in each of the three pre-defined characteristics of lesion visualization: contrast enhancement, border delineation and internal morphology. For each of these characteristics there was a pre-defined three point (zero to two) scoring scale. Lesion counting (up to five per patient) was also reflected in the overall score. The secondary endpoints included comparison of post-contrast to pre-contrast images, comparison to gadopentetate, confidence in a diagnosis and other analyses.

Of note, a comparison with an approved agent, gadopentetate (Magnevist), has served mostly as a validation for the reading methodology rather than a comparative effectiveness evaluation. Of further note, the scoring scale employed by Guerbet incorporates the lesion counting into the final score so that the finding of more lesions on paired images would tend to inflate a scoring advantage of paired over pre-contrast images in each of the visualization categories. Therefore, one has to be cautious, especially in cross-study comparisons, in interpreting the numerical values of Dotarem MRI image scores generated in the trial -050 and of the differences between such scores and baseline scores.

In this trial, efficacy was evaluated in 364 adults and 38 pediatric (age 2 and older) patients. Among adult patients, 245 received Dotarem and their data comprised the primary efficacy population. There were 114 (47%) men and 131 (53%) women with a mean age of 53 years (range 18 to 85 years), the racial and ethnic representations were 84% Caucasian, 11% Asian, 4% Black, and 1% other. The disease characteristics of this population were reflective of the intended use population.

All primary analyses, for each reader, demonstrated statistically significant superiority of Dotarem over non-contrast images, and these conclusions were supported by all pre-specified secondary analyses. The percentage of patients with improved lesion visualization for paired images compared to pre-contrast images ranged from 56% to 94% depending on a visualization category and a reader.

The performance of Dotarem in 38 pediatric patients (aged 2 years and older) for each reader and for each visualization category was similar to that seen in adults.

Study -051 was a re-read study of Dotarem MRI of the CNS performed earlier outside of US as a study -044. The demographics were generally similar to -050 although the primary clinical reviewer expressed a concern that the study was significantly under-representing African-American population. The concern appears to be somewhat mitigated by the belief that CNS disease and imaging patterns do not vary much by race. Of note, the original study -044 failed on the primary endpoints of sensitivity and specificity presumably because most of the patients had relatively large solitary neoplastic lesions so not much diagnostic advantage could be shown with the use of contrast. There were 150 patients in this study receiving Dotarem and there was no other imaging drug comparator. With the efficacy endpoints identical to the lesion visualization endpoints of the -050 trial the results of the -051 were supportive of the -050 results, with all analyses demonstrating the superiority of Dotarem for each reader and each lesion visualization category.

## **8. Safety**

The Dotarem clinical trial safety database is comprised of 2813 patients from 49 clinical trials. The age breakdown has been estimated by the applicant as 63% ages 18 to 65, 32% over 65 and 5% less than 18 years of age. Among them, about 4% have experienced adverse reactions, i.e. adverse events related to the drug. A similar observation was made in the main confirmatory trial -050.

Overall, most of the reported adverse events were considered to be mild and unrelated to Dotarem. There were no deaths or serious adverse events attributable to Dotarem except for a case of hypersensitivity and a case of an acute renal failure, both events described in association with other GBCAs. There were no cases of NSF. The most common adverse reactions in the clinical trial database occurring in over 0.2% of patients were nausea, headache and injection site reactions.

The non-US post-marketing experience is consistent with that for other GBCAs, except that Dotarem is the only GBCA with no un-confounded cases of NSF reported, so far. The

applicant estimates that approximately 30 million people around the world have received Dotarem.

The clinical review team has requested a Pharmacovigilance consultation from the Office of Surveillance and Epidemiology (OSE). The consult report summarized 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. The FAERS database contained 51 cases associated with Dotarem (47 adult cases and 4 pediatric, with 3 being less than 2 years of age). There were no reports of pediatric deaths or NSF cases in the pediatric population. A review of the literature by the OSE retrieved 13 articles related to the use of Dotarem in the pediatric population. The articles included approximately 1,203 pediatric patients administered Dotarem with 177 of these patients aged less than two years. None of the articles mentioned specific adverse events in any of the pediatric patients studied. The OSE review did not identify any new safety issues with Dotarem in either pediatric or adult populations.

## **9. Advisory Committee Meeting**

The meeting of the Medical Imaging Drug Advisory Committee was held on 2/14/2013 to address, among other things, the consideration of approval of Dotarem for use in pediatric patients less than two years of age.

The committee voted unanimously (17:0) for the finding of favorable “risk-to-benefit” assessment for use of Dotarem in CNS MRI among adults and pediatric patients aged two years and older. The committee voted against approving the drug for children younger than two years of age (10:6, with 1 abstention). Those who did vote for approval found the cited by the applicant historical data obtained outside US to be sufficient. The majority voted against approving Dotarem in infants and neonates for the paucity of clinical and pharmacokinetic data in this age group as well as for the lack of supportive juvenile animal data.

Other points made during the discussion period involved possible consideration of data from the currently ongoing safety study outside US (“Secure”), which has enrolled close to 80 patients less than two years of age, and a recommendation to assess the safety of GBCAs in premature infants. A concern was also raised about considering, in addition to the NSF, the whole safety profile and drug tolerability in this age group.

## **10. Pediatrics**

As mentioned in the Efficacy section above, the main confirmatory efficacy trial -050 has included 38 pediatric patients two years of age and older. Although not included in the primary efficacy analyses, the pediatric data were similar to those seen in the adults. In addition to these clinical trial data, the applicant submitted data from the three observational single-site studies (-15, -16, and -29), involving 99 pediatric patients. In these patients, data also showed an improved visualization obtained with Dotarem MRI. So altogether there are 137 pediatric patients in the clinical trial database. However, among these three studies, there are only seven patients less than two years of age.

In these 137 pediatric patients, Safety profile was comparable to the one seen in adults, demonstrating no new signals in this population. Of note, in more than half of all these patients, no laboratory values were available for review, and no pediatric pharmacologic data, such as blood pharmacokinetics or urinary excretion, have been obtained throughout Dotarem development program.

In spite of the mentioned limitations of the existing pediatric clinical trial database, relying on the overall clinical findings as well as general considerations related to imaging adult and pediatric CNS pathology, clinical team has recommended extrapolating safety and efficacy conclusions confirmed in the adult population to children two years of age and older. The same could not be concluded from the clinical trial database for children less than two years of age due to the insufficient data.

As supportive evidence, the applicant has submitted several publications, mostly in a summary format, describing postmarketing observational experience with the use of Dotarem outside US, which included close to 2500 pediatric patients, some less than two years of age. There is also a mention of an ongoing postmarketing safety study, "Secure", which reportedly includes over 80 patients less than two years of age. None of these data are available as source data for the FDA review and verification.

The applicant also makes a claim that approximately 52,000 children less than two years of age were exposed to gadoterate worldwide between 2005 and 2012. The number is an extrapolation from one year medical services utilization data in France not directly linked to utilization of this specific drug in this age group and could not be otherwise verified. It should be acknowledged, however, that, in this age group, no significant safety signals have been identified through the applicant's postmarketing pharmacovigilance reporting program.

## 11. Other Relevant Regulatory Issues

Good Clinical Practice (GCP) inspections involved the applicant (Guerbet headquarters), the imaging core lab (b) (4) and two clinical sites. No GCP violations were found.

There were no other relevant regulatory issues.

## 12. Labeling

At the time of the completion of this review the labeling review is still ongoing. The main revision of the labeling proposed by the applicant would include a change in the indicated population as the drug would not be approved for use in children less than two years of age. (b) (4)

(b) (4) The Clinical Studies section will emphasize the results from the main confirmatory clinical trial (-050). (b) (4)

### **13. Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

The Cross-Disciplinary Team Leader recommends approving Dotarem of use with MRI of the CNS in adults and children (age two years and older) and does not recommend an approval in younger children (neonates and infants). This is in line with the recommendations by other clinical and non-clinical reviewers and with the recommendation provided by the majority of the members of the MIDAC.

- Risk Benefit Assessment

The benefit of using a contrast agent with the MRI of the CNS is well accepted in the practice of medicine. An ability to visualize a normal or abnormal structure on an image is clinically useful. In that regard, the efficacy trials conducted by the applicant clearly demonstrate a superiority of Dotarem over a non-contrast MRI examination, with success shown in all pre-specified primary and secondary efficacy analyses by all imaging readers.

The risks of using GBCAs are well described at this time and are in general minimal in patients with normal renal function. A risk of the NSF is the biggest concern. Dotarem clearly belongs to the lower risk subgroup of this class of agents as it is the only drug in the class with no reports of un-confounded cases.

Therefore, in the risk/benefit assessment of Dotarem, the benefits clearly outweigh the risks for use in adults, with the labeling informing of a potential risk of the NSF. Similar conclusions can be extrapolated to the children two years of age and older based on the available data and general risks considerations including such factors as the maturity of the renal system.

The same cannot be said about the use of Dotarem in younger children with immature kidneys. Whereas the efficacy can be most likely extrapolated from data in adults and older children the amount of data relevant to using this drug in children less than two years of age is insufficient for evaluating the risk and therefore for making a favorable risk/benefit assessment.

- Recommendation for Postmarketing Risk Management Activities

In addition to labeling and routine pharmacovigilance, two Post-Marketing Requirements (PMRs) are being contemplated for Dotarem under PREA. One will involve an already ongoing non-clinical study in juvenile animals. The other will be a clinical safety and pharmacology study in children less than two years of age, most likely similar in design to the PMR for gadobutrol.

- Recommendation for other Postmarketing Study Commitments

There are no plans for other commitments.

Cross Discipline Team Leader Review  
NDA 204781 Dotarem  
Alex Gorovets, MD 031910

- Recommended Comments to Applicant

The comments will convey the approval of Dotarem for use in adults and children two years of age and older and the information on the PMRs for children less than two years of age.

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02/26/2013