CLINICAL REVIEW

Application Type	Pediatric Supplemental New Drug Application
Application Number(s)	NDA 204781 s001
Priority or Standard	Standard
Submit Date(s)	October 27, 2016
Received Date(s)	October 27, 2016
PDUFA Goal Date	August 27, 2017
Division / Office	DMIP/OND IV
Reviewer Name(s)	August Hofling, MD, PhD
Review Completion Date	July 27, 2017
Established Name	Gadoterate meglumine
(Proposed) Trade Name	Dotarem
Therapeutic Class	Diagnostic magnetic resonance imaging gadolinium-based contrast agent
Applicant	Guerbet LLC
Formulation(s)	0.5 M (376.9 g/L) solution
Dosing Regimen	0.2 mL/kg intravenously at flow rate of 1-2mL/second followed by saline flush
Indication(s)	For intravenous use with magnetic resonance imaging in brain (intracranial), spine and associated tissues to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
Intended Population(s)	Patients less than 2 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

We recommend approval of this first supplementary application to NDA 204781; specifically, that the central nervous system imaging indication for Dotarem 0.1 mmol/kg be extended to include all pediatric patients (including term neonates).

1.2 Risk Benefit Assessment

Our recommendation is primarily based on integration of the sponsor's current or previous submissions of preclinical, pharmacokinetic, and clinical safety and efficacy data as well as post-marketing experience with gadolinium-based contrast agents (GBCAs) in pediatric patients less than 2 years of age. This body of evidence shows no compelling reason why the favorable risk-benefit balance that established approval of Dotarem 0.1 mmol/kg in adults and older pediatric patients should not apply to pediatric patients younger than 2 years of age.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As the human kidney does not achieve its full number of nephrons until 36 weeks of gestation, it is reasonable to hypothesize that certain safety risks may be higher in premature infants compared to term infants. It is also possible that regulatory approval of Dotarem in term infants may lead to increased, albeit expectedly rare, off-label usage in premature infants. Thus, to assess potential need for labeling clarification and/or additional study, we propose to request comment by the sponsor on any observed change in Dotarem usage among premature infants in future quarterly safety updates and annual reports.

Additionally, to address the current lack of data that directly compares levels of gadolinium retention in pediatric and adult subjects, we suggest the sponsor performs a relevant preclinical study comparing delayed gadolinium measurements in tissues of juvenile and adult animals following Dotarem administration.

1.4 Recommendations for Postmarket Requirements and Commitments

We recommend updating to "fulfilled" the status of post-marketing requirement 2021-2. Specifically, study DGD-44-063 entitled, "Dotarem Pharmacokinetics, Safety, and Efficacy Study in Pediatric Subjects Aged <2 Years (Term Newborn Infants to Toddlers

23 Months of Age Inclusive)", fulfills requirement 2021-2. Requirement 2021-1 was fulfilled through study DGD-33-041 entitled, "Dotarem-neonatal and juvenile (pre-post weaning) toxicity study by the intravenous route in the rat", on November 5, 2014.

2 Introduction and Regulatory Background

2.1 Product Information

Dotarem is the trade name for gadoterate meglumine both domestically and abroad. It belongs to the gadolinium-based contrast agent (GBCA) pharmaceutical class. Molecules of this class incorporate the paramagnetic metal gadolinium (Gd^{3+}) that acts to reduce local relaxation times and produce enhancement on T1-weighted magnetic resonance imaging (MRI). GBCAs can be classified as ionic or non-ionic; linear or macrocyclic; non-, weakly, or strongly protein-binding; and FDA-labeled as relatively higher or lower risk of nephrogenic systemic fibrosis (NSF). Dotarem is a macrocyclic, ionic, non-protein-binding, relatively lower NSF-risk GBCA.

Dotarem was originally approved by the FDA as a new molecular entity (NME) on March 20, 2013. It was the last of the currently nine GBCAs approved for marketing in the United States as listed by order of approval: Magnevist (1988), Prohance (1992), Omniscan (1993), Optimark (1999), Multihance (2004), Eovist (2008), Ablavar (2008), Gadavist (2011), and Dotarem (2013). Dotarem was approved for use in France in 1989 and has subsequently obtained approvals in more than 80 countries.

In language taken from its FDA label, Dotarem is currently indicated for "intravenous use with MRI in brain (intracranial), spine, and associated tissues in adult and pediatric patients (including term neonates 2 years of age and older) to detect and visualize areas with disruption of the blood-brain barrier (BBB) and/or abnormal vascularity." The currently indicated dose is 0.2 mL/kg (0.1 mmol/kg) of the 0.5 mmol/mL solution administered as an intravenous bolus injection. The sponsor now seeks extension of its central nervous system (CNS) imaging indication to all pediatric patients, including term neonates, with the same dose.

2.2 Tables of Currently Available Treatments for Proposed Indications

Out of the seven GBCAs approved for MRI of the CNS, only Gadavist is approved in pediatric patients younger than 2 years of age. Dotarem is currently indicated in pediatric patients aged 2 years and up. Table 1 lists the GBCAs approved for MRI of the CNS and their respective pediatric labeling.

Table 1: Reviewer's tabulation of currently available contrast agents for MRI of the CNS

Proprietary Name	Non-proprietary Name	FDA-approval for Pediatric CNS MRI
Magnevist	gadopentetate dimeglumine	Age ≥ 2 years
Prohance	gadoteridol	Age ≥ 2 years
Omniscan	gadodiamide	Age ≥ 2 years
Optimark	gadoversetamide	None
Multihance	gadobenate dimeglumine	Age ≥ 2 years
Gadavist	gadobutrol	Term neonates and older
Dotarem	gadoterate meglumine	Age ≥ 2 years

Outside of the United States, Dotarem is approved for CNS imaging in pediatric patients younger than 2 years of age in all countries in which it is approved for adults, with the exception of Japan where it is only approved in adults and Singapore where it is only approved in adults and children aged 2 to 18 years.

2.3 Availability of Proposed Active Ingredient in the United States

Dotarem is the only marketed drug in the United States that contains gadoterate meglumine.

2.4 Important Safety Issues with Consideration to Related Drugs

Gadolinium Retention

Review of new indications for GBCAs at this time must consider the accumulating evidence of long-term retention of gadolinium in various tissues of animals and patients with normal renal function following GBCA administration. For the purposes of this discussion, the term retention will be used to distinguish this process from that of nephrogenic systemic fibrosis (NSF), which by definition only occurs in the setting of renal impairment following GBCA administration. In contrast to NSF, the now well documented chronic retention of gadolinium in animals and patients with normal renal function has only rare and mechanistically unclear association with nonspecific clinical consequences at the time of this review.

However, the current lack of consensus regarding clinical effects does not exclude the possibility of toxicity related to gadolinium retention. One can also hypothesize that such potential toxicity, if any, may be more pronounced in the rapidly developing neonatal and infant population. Continued attention to the subject of gadolinium retention is clearly warranted as indicated in a recent FDA Drug Safety Communication update on May 22, 2017, that specifically addresses evidence of this process in the brain. For the time being, a proactive strategy to mitigate this potential safety issue includes selection

of GBCAs that are associated with lower levels of gadolinium retention as well as judicious use of these GBCAs.

The body of available data in animals and humans to date, as recently reviewed by Tedeschi and colleagues (Radiol Med 2017; 122:589-600), indicates generally lower levels of gadolinium retention associated with macrocyclic GBCAs compared to linear GBCAs. Further differentiation among currently approved macrocyclic GBCAs for their relative propensity for gadolinium retention is not well established at this time though. However, as the only GBCA in clinical use that is both macrocyclic and ionic, Dotarem is reported to have among the highest thermodynamic and kinetic stability as measured *in vitro*, suggestive but not necessarily indicative of greater *in vivo* stability (Hao et al., J Magn Reson Imaging 2012; 36:1060-1071). While comparative *ex vivo* quantitation of gadolinium retention in human tissues following Dotarem administration has not been published at this time, available animal data confirms that levels of retention associated with Dotarem are similar to those of other macrocyclic agents including Gadavist, the only other GBCA currently approved for use in pediatric patients under 2 years of age (Pietsch et al., Eur Radiol 2009; 19:1417-1424).

The perception of Dotarem's safety profile among pediatric practitioners was elucidated in a recent publication by Mithal and colleagues (Pediatr Radiol 2017; 47:657-664). Of 26 North American pediatric radiology departments surveyed, 15 departments (58%) changed the type of GBCA they used in the year between early 2015 and early 2016 due predominantly to gadolinium safety concerns. Of these 15 pediatric radiology departments, most (53%) switched to Dotarem with 20% of them switching from Gadavist to Dotarem. Similarly, 6 of 26 (23%) pediatric radiology departments indicated that they were considering changing the type of GBCA used within the year following early 2016, again typically due to gadolinium safety concerns, with most of these departments (83%) intending to switch to Dotarem.

Although comparative studies have identified lower levels of gadolinium retention associated with macrocyclic agents compared to linear agents, it is generally accepted that all currently approved GBCAs including macrocyclic agents will result in some degree of chronic gadolinium retention. Dotarem appears to be no exception with, for example, low but measurable levels of gadolinium detectable in brains of healthy adult rats 5 weeks following administration of multiple doses of Dotarem (Robert et al., Invest Radiol 2015; 50:473-480) and in other tissues of healthy juvenile rats 1 week following administration of multiple doses of Dotarem (Fretellier et al., Reprod Toxicol 2014; 50:171-179). In the only published study at this time to demonstrate gadolinium retention in tissues of humans without significant renal impairment following Dotarem administration, Maximova and colleagues measured low levels of gadolinium for extended periods of time in the liver of children who underwent hematopoietic stem cell transplantation and subsequently received Dotarem injection (Radiology 2016; 281:418-426).

While the potential clinical consequences of gadolinium retention are uncertain at this time, it remains clear that use of GBCAs to enhance MRI is clinically valuable in many situations, including in certain pediatric patients younger than two years of age. When appropriately administered, MRI performed with GBCAs can provide critical diagnostic information that often cannot be obtained through noncontrast MR images alone or through other imaging modalities. While CT performed with iodinated contrast can sometimes yield diagnostic information comparable to GBCA-enhanced MRI, it does so at the expense of significant ionizing radiation, a known safety issue particularly for pediatric patients. Thus, in situations when anticipated diagnostic benefit is high, use of a GBCA would appear to outweigh any unproven or sufficiently rare risk of gadolinium retention. This rationale is mirrored in the original 2015 FDA Drug Safety Communication regarding gadolinium retention in the brain, which states that "health care professionals should consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary."

Evidence of such judicious use of GBCAs does exist, particularly in the pediatric population. A recent publication by Blumfield and colleagues concluded that use of GBCAs in children was generally concordant with American College of Radiology Appropriateness Criteria, as supported by a survey of Society for Pediatric Radiology members based predominantly at U.S. academic centers (Pediatr Radiol 2017; 47:665-673). Reflecting further evidence of judicious use, GBCA administration in pediatric subjects younger than two years of age is estimated to be relatively infrequent compared to adults and older children. At a meeting of the FDA Center for Drug Evaluation and Research Medical Imaging Drugs Advisory Committee on February 14, 2013, that was focused on whether initial marketing approval for Dotarem should include pediatric patients younger than age 2 years, it was estimated that roughly 20,000 patients in this age range per year receive GBCAs for MRI in the United States. At the time of the meeting, this estimated use was entirely off-label as Gadavist was not yet approved in pediatric patients less than two years of age. Approval of Dotarem in children younger than two years of age is not anticipated to result in an increase in usage in this patient population.

Nephrogenic systemic fibrosis (NSF)

While distinguished by its occurrence only in the setting of renal impairment, NSF is gadolinium induced. As such, FDA classification of Dotarem as one of the GBCAs with less association with NSF can be seen as further support for its favorable profile regarding gadolinium retention. In fact, information contained in the sponsor's submission as well as post-marketing data collected by the FDA at this time demonstrate no clearly confirmed cases of NSF following Dotarem administration that are "unconfounded", or lacking additional history of administration of other GBCAs. At least one report of possible NSF following potentially exclusive administration of Dotarem does exist, however, and other unconfounded cases could presumably be described in the future.

Labels for all of the approved GBCAs continue to carry one of two boxed warning variants regarding NSF. These boxed warnings separate GBCAs into two groups based upon NSF risk and also provide recommendations regarding renal function screening. Encouragingly, the publication of these boxed warnings has been associated with a decline in new cases of NSF in recent years. The label for Dotarem and other GBCAs associated with NSF at a relatively lower rate (Multihance, Prohance, Eovist, Ablavar, and Gadavist) carry a boxed warning as appears in the following indented text:

> WARNING: NEPHROGENIC SYSTEMIC 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.
>
> - The risk for 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 (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.

The label for GBCAs associated with NSF at a relatively higher rate (Magnevist, Omniscan, and Optimark) carry the following boxed warning with text differing from the above warning shown in italics:

> WARNING: NEPHROGENIC SYSTEMIC 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.
>
> - *Do not administer [GBCA] to 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 (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2 provides a timeline of the FDA regulatory history pertaining to pediatric use of Dotarem, based on the sponsor's summary and review of referenced regulatory database submissions.

Table 2: Reviewer's tabulation summarizing Dotarem's relevant FDA regulatory history

Date	Application	Description
6/13/2002	IND 65041	Original IND received from Paraxel International
11/1/2002	IND 65041	Sponsor changed to Guerbet LLC
7/28/2010	IND 65041	Special Protocol Agreement accepted for phase III protocol DGD-44-050 including pediatric patients aged 2 years and older
2/10/2013	NDA 204781	Primary clinical review of NDA submission
2/14/2013	NDA 204781	Medical Imaging Drugs Advisory Committee meeting held
3/6/2013	NDA 204781	Pediatric Review Committee meeting held
3/20/2013	NDA 204781	Marketing approval for Dotarem's CNS indication in patients older than 2 years of age, including deferred pediatric post-marketing requirements (PMRs) for animal (2021-1) and human pharmacokinetic (2021-2) studies in patients younger than 2 years of age, per the Pediatric Research Equity Act (PREA; 21 U.S.C. 355c)
10/31/2013	IND 65041	PMR 2021-2: final protocol received for pharmacokinetic/efficacy study DGD-44-063
3/5/2014	IND 65041	PMR 2021-2: clinical pharmacology agreement on DGD-44-063 study design
8/1/2014	NDA 204781	PMR 2021-1: final preclinical review of neonatal and juvenile rat study report DGD-33-041
11/5/2014	NDA 204781	PMR 2021-1: fulfillment letter
10/27/2016	NDA 204781	Application for pediatric sNDA efficacy supplement and fulfillment of PMR 2021-2 received

During FDA review of NDA 204781 for initial approval of Dotarem, a Medical Imaging Drugs Advisory Committee held on February 14, 2013, unanimously agreed that the available data supported approval in adults and children aged 2 years and over. However, most committee members felt that safety data was inadequate in pediatric

subjects less than 2 years of age, citing that the available clinical trial database included only 7 of such subjects in this age group. Despite estimates that roughly 51,000 subjects under 2 years of age had been exposed to Dotarem worldwide at that time, the consensus recommendation was for additional clinical safety data in this age group as well as additional nonclinical data in juvenile animals.

As such, Dotarem was approved for a CNS imaging indication in adults and children of at least 2 years of age with required pediatric assessments as quoted from the FDA approval letter below.

- Study 2021-1: Provide additional nonclinical (animal) data to support the safety of your product in the 0-23 month pediatric age group. These nonclinical data should be obtained from newborn to juvenile animals that model pediatric patients in this age group. The study will examine the safety of the product in newborn and neonates animals, following a single dose and limited repeated dose administrations.
    - Draft Protocol Submission: December 2012 (completed)
    - Final Protocol Submission: March 2013
    - Study/Trial Completion: September 2013
    - Final Report Submission: December 2013

- Study 2021-2: Examine patients 0-23 months of age who are referred for an MRI exam with contrast. A sufficient number of subjects will be studied to adequately characterize the pharmacokinetics of the product in this age group. At least 40 patients will be evaluated in this study, and the study must include a sufficient number of subjects to adequately support the safety and efficacy of Dotarem for central nervous system MRI.
    - Draft Protocol Submission: August 2013
    - Final Protocol Submission: October 2013
    - Study/Trial Completion: June 2015
    - Final Report Submission: June 2016

2.6 Other Relevant Background Information

Dotarem was first approved in France in March of 1989 for MRI of the CNS. It has since been approved in over 80 countries outside of the US. In addition to CNS imaging, approved foreign indications for Dotarem are magnetic resonance angiography (MRA) including carotid and vertebral MRA and MRI of the whole body including liver, pancreas, kidney, and breast. In most foreign countries, Dotarem is approved for use in adult and pediatric patients, including neonates and infants. In Japan, the drug is marketed under the trade name Magnescope. A dilute formulation of gadoterate meglumine specifically intended for arthographic injection is marketed in several countries outside the US under the trade name Artirem.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Based on filing review on December 13, 2016, the sponsor's application was found to be sufficiently complete to allow substantive review. The sponsor was notified on December 22, 2016.

3.2 Compliance with Good Clinical Practices

The sponsor reports adherence to the principles of Good Clinical Practice, including those outlined in the International Council for Harmonization (E6) and in keeping with study-subject protection as outlined in the Declaration of Helsinki and subsequent amendments.

3.3 Financial Disclosures

The sponsor reports adequate collection of financial interest forms with no disclosable information from all principal investigators and sub-investigators who enrolled study subjects.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

(b) (4)

4.3 Preclinical Pharmacology/Toxicology

In study DGD-33-041, the sponsor reported that all tested dose levels showed no significant treatment effects after either single dose or limited repeated dose administrations in juvenile rats aged 10 or 30 days. Based on preclinical review, the estimated no-observed-adverse-effect level was 2.5 mmol/kg. After a 60-day treatment-free period following a single dose administration, trace levels of gadolinium were found

in the kidneys of some animals. After a 60-day treatment-free period following repeated dose administration, detectable levels of gadolinium were found in the kidneys of most animals and trace gadolinium levels were found in the bone and liver of a few animals in the highest dose cohort. In animals that were sacrificed immediately after single or repeated dosing, tissue gadolinium levels were measurable in a dose-dependent manner in bone, skin, liver, and kidney. Other tissues such as brain were not tested.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The gadolinium ion within each Dotarem molecule is paramagnetic with seven unpaired electrons that enable a high magnetic moment. Gadolinium shortens the T1 and T2 relaxation times of local water protons in blood and tissues through a concentration-dependent property termed relaxivity. Shortening of T1 relaxation time leads to high signal intensity, also known as enhancement, on T1-weighted MRI images. As an extracellular contrast agent, this enhancement can improve visualization of vessels, vascular lesions, and areas of blood-brain barrier breakdown.

4.4.2 Pharmacodynamics

Dotarem is physiologically inert and distributes passively in the blood and extracellular fluid. It is excreted by the kidneys into urine. Timing of image acquisition relative to Dotarem injection determines its localization on static images. The distribution of Dotarem in the brain is also impacted by pathological disruption of the blood-brain barrier.

4.4.3 Pharmacokinetics

Dotarem in not metabolized and is eliminated by the kidneys through glomerular filtration with negligible extrarenal elimination. The mean half-life in blood is 1.6 hours in humans with normal renal function.

New clinical pharmacokinetic data submitted with this application includes study DGD-44-063 on subjects younger than 2 years of age and study DGD-44-054 on adults with end-stage renal failure requiring hemodialysis. Analysis of the primary pharmacokinetic endpoints of these studies appears in the separate clinical pharmacology review of this application.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 lists the studies relevant to analysis of CNS imaging efficacy in pediatric subjects less than 2 years of age.

Table 3: Listing of studies relevant to imaging efficacy evaluation in this sNDA

Trial Identity	Study Population (less than 2 years of age with Dotarem-enhanced CNS imaging)	Imaging evaluation
Main safety and efficacy clinical study (PK study)		
DGD-44-063	28	Pre- vs. pre- and post-contrast
Supportive clinical studies		
DGD-03-015	3	Pre- vs. post-contrast
DGD-03-016	2	Pre- vs. post-contrast
DGD-03-029	2	Pre- vs. post-contrast
Post-marketing surveillance studies		
DGD-55-001	85	Post-contrast alone
DGD-55-002	85	Post-contrast alone

5.2 Review Strategy

This review focuses on safety data and the secondary CNS imaging efficacy endpoints of the sponsor's trials in pediatric subjects less than two years of age. Analysis of primary pharmacokinetic endpoints in main study DGD-44-063 is detailed in the separate clinical pharmacology review. Secondary efficacy endpoints based on diagnostic imaging interpretation in main study DGD-44-063 and other supporting trials were neither designed nor statistically powered to guide regulatory decisions on an independent basis. Rather, they were assessed for their level of support in extrapolating higher quality imaging efficacy evidence in adults and older children. Sections of the review template relevant only to an original NDA were omitted.

6 Review of Efficacy

Efficacy Summary

Methodological deficiencies in main study DGD-44-063 described at the end of section 6.1.1 as well as the relatively small number of subjects with evaluable CNS lesions limit the ability to confidently make independent inferences about the CNS imaging efficacy of Dotarem in pediatric patients younger than 2 years of age. However, in light of more definitive existing adult efficacy data, the primary pharmacokinetic endpoints of this pediatric supplemental application, the known mechanism of GBCA action, and the inherent challenges of pediatric research, the sponsor's limited but directional imaging interpretation data favor extrapolation of CNS imaging efficacy to pediatric patients less than 2 years of age.

6.1 Indication

The label for Dotarem currently indicates one use, as appears in the following indented text:

> 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 (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

The sponsor proposes the following change for this CNS indication as shown in italics:

> 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 (*including term neonates*) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

6.1.1 Methods

Pivotal efficacy assessment relies on the report for study DGD-44-063 dated May 30, 2016, entitled, "Dotarem Pharmacokinetics, Safety, and Efficacy Study in Pediatric Subjects Aged <2 Years (Term Newborn Infants to Toddlers 23 Months of Age Inclusive)." The primary objective of this trial was to evaluate the plasma pharmacokinetics profile of Dotarem in the target age group following a single intravenous injection. Secondary objectives were evaluation of safety for up to 7 ± 1 days following injection in this study population as well as evaluation of CNS imaging efficacy in a relevant subgroup.

DGD-44-063 study design was multicenter, open-label, non-randomized, and single group. Five inclusion criteria and 12 exclusion criteria were employed. Main entry criteria consisted of term newborn infants (defined as ≥ 37 weeks amenorrhea) to toddlers 23 months of age inclusive who were scheduled to have a routine enhanced MRI of any body region with a GBCA dose of 0.1 mmol/kg.

An additional notable inclusion criterion was the requirement for "normal eGFR for age", where eGFR denotes estimated glomerular filtration rate. The measurement of eGFR in younger children is complicated by lack of an accepted normal reference range in this population and lack of meaningful comparability of eGFR normalized to body surface area in younger children relative to older children and adults. The sponsor used the Schwartz formula to calculate eGFR which includes height, age, and serum creatinine as inputs. Minimum acceptable eGFR levels set by the sponsor for various age groups were approximately two standard deviations below the mean values compiled by Schwartz and Furth from multiple references that measured inulin clearance (Pediatr Nephrol 2007; 22:1839-1848). Table 4 displays the calculated eGFR ranges that the sponsor required for inclusion in study DGD-44-063.

Table 4: Sponsor's normal eGFR ranges for inclusion in main study DGD-44-063

Age	eGFR normal range (mL/min/1.73 m²)
Day 1 – day 3	> 10
Day 4 – day 14	> 22
Day 15 – 3 months	> 25
4 months – 6 months	> 42
7 months – 2 years	> 60

Use of cut-off values two standard deviations below published mean values would appear to allow some degree of generalization of the study protocol to potential clinical practice. Of note, all of the cut-off values selected by the sponsor as listed in table 4 are lower than those used for inclusion in the pivotal trial that allowed approval of Gadavist for CNS imaging in children younger than two years of age.

Complete inclusion and exclusion criteria for main study DGD-44-063 are quoted from the clinical study report below:

Inclusion criteria:
1. Pediatric subject aged <2 years (term newborn infants to toddlers 23 months of age inclusive); term is defined as ≥37 weeks of amenorrhea.

2. Subject is scheduled to undergo routine gadolinium-enhanced MRI of any body region (e.g. CNS, cardiac) at the dose of 0.1 mmol/kg body weight (0.2 mL/kg body weight).
3. Subject with normal renal function for its age according to estimated glomerular filtration rate calculated based on the Schwartz formula.
4. Subject whose parents or legal guardian (where applicable) has/have provided his/her/their fully informed written consent for the participation of the child in the trial. Parents or guardian had to have the ability to read, understand and willingness to sign the informed consent form.
5. Subject with health insurance, according to the local regulatory requirement.

Exclusion criteria:
1. Subject planned for intervention (e.g. surgery) between the screening visit and up to 24 hours after Dotarem injection.
2. Subject whose preceding or subsequent treatment to Dotarem injection (e.g., blood loss or receiving blood, treatment with diuretics, etc.) would alter Dotarem pharmacokinetics parameters.
3. Subject with subsequent planned treatment after Dotarem injection that would prevent obtaining the required blood samples (e.g., emergency surgery, etc.).
4. Subject with a history of a bleeding disorder.
5. Subject with known severe liver disease.
6. Subject with electrolyte or fluid imbalance that presents undue risk.
7. Subject undergoing a change in chemotherapy within 48 hours prior to and up to 24 hours after Dotarem injection.
8. Subject who received or will receive any other contrast agent within 72 hours prior to Dotarem injection or up to 24 hours after Dotarem injection.
9. Subject with contraindication to MRI such as iron metal implants (e.g. aneurysm clips).
10. Subject with history of anaphylactoid or anaphylactic reaction to any allergen including drugs and contrast agents.
11. Subject who received or will receive any investigational product within 7 days before Dotarem injection or during study participation.
12. Any condition which, based on the investigator's clinical judgment, would prevent the subject from participating in all study assessments and visits.

Study participation took place over four separate subject-study interactions. The first visit was for screening and took place within two weeks of the second visit for inclusion. Injection of Dotarem and subsequent MRI occurred during the second visit as well as collection of three blood samples for pharmacokinetics at a randomized time within in each window of 10 to 60 minutes, 2 to 4 hours, and 6 to 8 hours. The third visit consisted of an onsite safety follow-up at 24 ± 4 hours after Dotarem injection. The fourth interaction consisted of a follow-up visit or phone call for delayed adverse event monitoring 7 ± 1 days following Dotarem administration. A flow chart of subject-study interactions appears in Figure 1 below.

Figure 1: Sponsor's schedule of procedures in main study DGD-44-063 (from Table 9.1 of Clinical Study Report)

Visit for the subject	**Screening Visit**	**Inclusion Visit**					**Safety Follow-up Visit**	**Safety follow-up Contact**
Visit number	**1**	**2**					**3**	**4**
Day	**D-14 to D0**	**D0**					**D1**	**D7 +/-1d**
Time		**Before injection**	**T0 injec-tion**	**T 10min to 60min**	**T 2h to 4h**	**T 6h to 8h**	**T24h +/-4h**	
Informed Consent	X							
Inclusion / non-inclusion criteria	X	X						
Management of Inclusion - IWRS (1)		X						
Demographic information	X							
Medical / surgical history	X							
Concomitant treatments	**assessed throughout the period**							
Urinalysis (dipstick)	X						X	
Blood samples for central lab tests (2)	X						X	
eGFR (Schwartz formula)	X (3)						X	
Physical Examination, Body Weight, Height	X							
Vital signs (4)		X	X		X		X	
Injection site tolerance monitoring			**assessed throughout the period**					
Adverse Event	**assessed throughout the period**							
IMP administration			X					
MRI examination			X					
Blood samples for PK (5)				X	X	X		

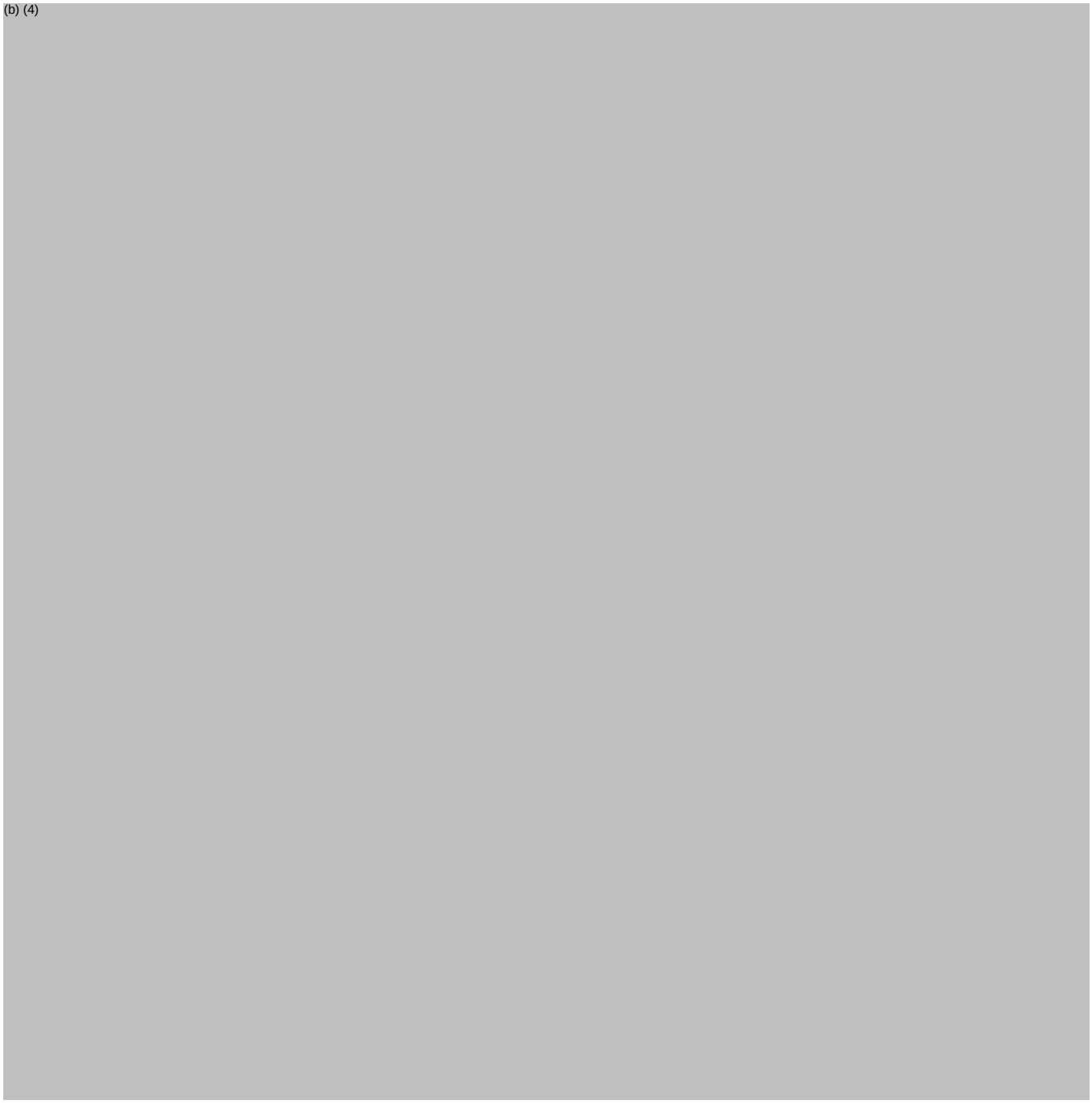
Image interpretation endpoints were secondary to pharmacokinetic endpoints in main study DGD-44-063 and were collected only for MRI studies of the CNS. For both pre-contrast images and combined pre- and post-contrast images, readers had to indicate whether images were assessable (yes or no) and indicate the reason if images were not assessable. Overall image quality was also scored separately on a 3-point scale for both pre-contrast images as well as the combination of pre- and post-contrast images. Other data consisted of surveys for 3 lesion visualization endpoints (border delineation, internal morphology, and contrast enhancement) scored by a single on-site radiologist for each subject's MRI. Up to 5 of the largest lesions in each subject were individually scored separately on pre-contrast images alone as well as the combination of pre- and post-contrast images using a 3-point scale for the 3 visualization endpoints.

Regions of interest (ROIs) were additionally placed by the site radiologist to allow calculation of signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) for lesions on both pre- and post-contrast T1-weighted images. SNR calculations involved correction of measurements within lesions for background imaging noise while CNR calculations involved correction of measurements within lesions for signal in healthy tissue. While ROIs placed on pre-contrast images automatically registered on corresponding post-contrast images, readers were able to manually adjust ROI positions independently for perceived misregistration. Readers were also instructed to make ROI sizes as large as could possibly be placed in homogeneous areas.

Excerpts from the case report form that was separately completed by a site-radiologist for each set of pre-contrast images alone as well each set of combined pre- and post-contrast images for each CNS MRI in study DGD-44-063 appear below in Figure 2.

Figure 2: Excerpts from case report form for main study DGD-44-063

(b) (4)



(b) (4)

Certain methodological weaknesses limit the validity of imaging interpretation endpoints by introducing elements of potential imaging variability. Image acquisition itself was performed on scanners of varying manufacturer, model, and field strength. Local scanning protocols at each site also dictated the exact imaging sequences acquired and therefore likely differed to some degree.

Additional methodological weaknesses introduce potential bias into imaging interpretation endpoints. In addition to referral bias, sources of potential bias among site-readers were present. Completion of case report forms by site-radiologists may

have occurred while they were generating clinical reports for the purposes of patient care. Interpreting radiologists were further aware of the purpose of the study and the identity of the pre- and post-contrast images. Also, assessment of endpoints on a 3-point scale is essentially a subjective determination. Although calculation of SNR and CNR is more objective, variable placement or sizing of ROIs could yield poorly representative results. Use of only one reader for each subject's MRI also limits quality of the data collected.

6.1.2/3 Demographics/Subject Disposition

For main study DGD-44-063, the sponsor reports nested subject groups of size n=51 (enrolled), n=47 (randomized for PK), and n=45 (treated and completed study). Of the n=51 enrolled group, four subjects were not randomized for PK due to consent withdrawal (n=1), adverse event (n=1), and completion of the age group (n=2). Of the resulting n=47 group, two subjects did not receive contrast due to consent withdrawal (n=1) and adverse event (n=1).

Of the n=45 treated group, eight protocol deviations were reported and described by the sponsor as non-major. One subject received commercial Dotarem instead of the investigational product. One 19.1 month-old subject undergoing MRI of anatomy other than the CNS received 1.5 mL of investigational product instead of the correct weight-adjusted dose of 2.0 mL. In three subjects, the assigned PK sampling time window was not respected. In two subjects, baseline serum creatinine was below the lower limit of quantification at screening and eGFR was calculated using the lower limit value of 0.17 mg/dL. In one subject, two blood samplings were conducted during the screening period instead of one.

In study DGD-44-063, nine centers enrolled 51 subjects across four countries including Poland (n=32), Hungary (n=11), France (n=5), and Austria (n=3). Of note, the international setting of this main study does not appear to present any significant concerns regarding applicability of results to the U.S. population. The n=45 treated group ranged in age from less than one week to 23.8 months with 22 male and 23 female subjects. A planned nonuniform age distribution was achieved with 5 subjects aged 0-1 month, 9 subjects aged 1-3 months, and 31 subjects aged 3-23 months. Baseline eGFR was missing for 2 subjects, one aged 1.7 months and the other aged 15.7 months. The lowest measured eGFR values at baseline were collected in a subject less than 1 week of age (52 ml/min/1.73 m^2) and a subject 2 weeks of age (54 ml/min/1.73 m^2). All other collected baseline eGFR measurements exceeded 60 ml/min/1.73 m^2. The n=45 treated group was predominantly white (95.6%). Of the n=45 treated group which served as the safety and pharmacokinetic set, 28 were referred for MRI imaging of the brain, spine, or head/neck and served as the evaluable efficacy set. Table 5 provides the sponsor's demographic summary of these study sets.

Table 5: Sponsor's summary of demographic data in subjects less than 2 years of age who received Dotarem in main study DGD-44-063 (from Table 6 of Clinical Summary of Efficacy)

	All Analyzed Patients N=45	All Patients Evaluable for Efficacy N=28
Age (months)		
Mean (SD)	9.88 (7.36)	8.21 (7.19)
Median (min; max)	9.3 (0.0; 23.8)	5.7 (0.0; 23.8)
Age (in categories), N (%)		
≤30 days	5 (11.1%)	5 (17.9%)
≥31 days and ≤90 days	9 (20.0%)	6 (21.4%)
≥91 days and <2 years	31 (68.9%)	17 (60.7%)
Sex, N (%)		
Male	22 (48.9%)	15 (53.6%)
Female	23 (51.1%)	13 (46.4%)
Race, N (%)		
Black or African American	1 (2.2%)	1 (3.6%)
White	43 (95.6%)	27 (96.4%)
Other	1 (2.2%)	0 (0.0%)
Weight (kg)		
Mean (SD)	8.1 (3.1)	7.6 (3.5)
Median (min; max)	8 (3; 15)	7 (3; 15)
Height (cm)		
Mean (SD)	68.8 (11.5)	66.8 (12.3)
Median (min; max)	71 (47; 87)	64 (47; 87)
Body Mass Index (kg/m²)		
Mean (SD)	16.5 (2.7)	16.1 (3.2)
Median (min; max)	17 (12; 25)	16 (12; 25)
MRI Indication, N (%)		
CNS	28 (62.2%)	28 (100.0%)
- Brain (intracranial)	24	24
- Spine	7	7
- Associated tissues (head and neck)	4	4
Whole Body	4 (8.9%)	1 (3.6%)
MSK	5 (11.1%)	1 (3.6%)
Abdomen	7 (15.6%)	1 (3.6%)
Other	7 (15.6%)	0 (0.0%)

Abbreviations: CNS, central nervous system; max, maximum; min, minimum; MRI, magnetic resonance imaging; MSK: musculoskeletal; SD, standard deviation.

6.1.4 Analysis of Imaging Endpoint(s)

In study DGD-44-063, all MRI images of the CNS from all 28 subjects of the efficacy group were rated as assessable by site radiologists. Of note, 75% of the 28 subjects were imaged on 1.5 T scanners while 25% were imaged on 3 T scanners. Among choices of “good”, “fair”, or “poor”, the overall pre-contrast image quality was rated “good” for 26 subjects and “fair” for 2 subjects whereas overall image quality was rated as “good” in all 28 subjects for combined pre- and post-contrast images.

Of the 28 subjects who underwent MRI for CNS indications, lesions were identified on pre-contrast images in 15 subjects and on combined pre- and post-contrast images in 16 subjects. Aside from the single discrepant subject in whom 2 lesions were seen only on post-contrast images and not on pre-contrast images, the same number lesions were seen on pre- and post-contrast images of all other 15 subjects.

In subjects with lesions, a single lesion was most commonly found (62.5% of subjects), with the maximum number ranging up to 11 lesions in one subject. This subject with 11 lesions was the only subject in whom all lesions were not assessed for imaging endpoints, with the five largest lesions being evaluated and the smaller 6 lesions being unevaluated. All other subjects had 5 or less lesions, with all of them being evaluated.

In total, visualization endpoints were analyzed for 28 lesions identified in 15 subjects on pre-contrast images and 30 lesions identified in 16 subjects on combined pre- and post-contrast images. Of the 30 lesions identified on combined pre- and post-contrast images, 27 (90%) were assessed as displaying at least some degree of enhancement. The superlative descriptor for lesion border delineation was assigned to 11 of 28 (39.3%) lesions on pre-contrast images and 22 of 30 (73.3%) lesions on combined pre- and post-contrast images. The superlative descriptor for internal morphology was assigned to 14 of 28 (50%) lesions on pre-contrast images and 23 of 30 (76.7%) lesions on combined pre- and post-contrast images. Of note, scores for all visualization endpoints did not worsen for any of the identified lesions on combined pre- and post-contrast images compared to pre-contrast images. Data for the three lesion visualization co-endpoints appear in table 6 below, presented by the sponsor at the lesion level.

Table 6: Lesion visualization endpoints at the lesion level for main study DGD-44-063 (from Table 11.9 of Clinical Study Report)

	Pre-contrast (N=28 lesions)*	Pre+Post contrast (N=30 lesions)*
Lesion border delineation score		
1-None	2 (7.1%)	0 (0.0%)
2-Moderate	15 (53.6%)	8 (26.7%)
3-Clear and complete	11 (39.3%)	22 (73.3%)
Internal morphology score		
1-Poorly visible	5 (17.9%)	0 (0.0%)
2-Moderately visible	9 (32.1%)	7 (23.3%)
3-Sufficiently visible	14 (50.0%)	23 (76.7%)
Contrast enhancement score		
1-None	28 (100.0%)	3 (10.0%)
2-Weak	0 (0.0%)	4 (13.3%)
3-Clear and bright	0 (0.0%)	23 (76.7%)

At the subject level, in the 16 patients that had identifiable lesions, scores were improved for at least one lesion on combined pre- and post-contrast images compared to pre-contrast images in 8 out of 16 (50%) patients for lesion border delineation, 8 out of 16 (50%) patients for lesion internal morphology, and 14 out of 16 (88%) patients for lesion contrast enhancement. These calculations consider the one subject who had lesions identified only on post-contrast images as improved for all 3 lesion visualization endpoints.

Signal intensity measurements were collected for all 28 lesions identified on pre-contrast images but only 29 of the 30 lesions identified on post-contrast images due to lack of recorded measurements for one of these post-contrast lesions. Mean (± standard deviation) SNR increased from 112.3 (± 57.8) for lesions on pre-contrast images to 212.6 (±198.3) on post-contrast images. Mean (± standard deviation) CNR increased from 9.3 (±27.8) for lesions on pre-contrast images to 79.4 (±109.9) on post-contrast images. SNR and CNR data presented by the sponsor at the lesion level appears in table 7 below.

Table 7: SNR and CNR at lesion level for main study DGD-44-063 (from Table 11.11 of Clinical Study Report)

		Pre-contrast (N=28 lesions)*	Pre+Post contrast (N=30 lesions)*
SNR	n	28	29
	Mean (SD)	112.3 (57.8)	212.6 (198.3)
	Median	108	144
	Min ; Max	27 ; 268	51 ; 1061
	Missing	0	1**
CNR	n	28	29
	Mean (SD)	9.3 (27.8)	79.4 (109.9)
	Median	11	51
	Min ; Max	-53 ; 89	-25 ; 561
	Missing	0	1**

6.1.10 Additional Efficacy Issues/Analyses

Three supportive, non-randomized studies (DGD-03-015, DGD-03-016, and DGD-03-029) included 7 pediatric subjects of less than 2 years of age, all of whom received Dotarem for CNS imaging indications. In each of these 7 patients, the sponsor provides brief narrative accounts of the added value of post-contrast images relative to pre-contrast images such as confirmation of the absence of a lesion, improvement in lesion visualization, or improvement in lesion characterization.

7 Review of Safety

Safety Summary

Of the 52 pediatric subjects less than two years of age that were exposed to Dotarem in clinical trials, only a single adverse event of rash was thought to be drug-related. Rash is also one of the more common adverse reactions in the general population. The limited number of adverse reactions reported from clinical studies and postmarketing surveillance in patients less than two years of age otherwise limits direct comparison to safety data from older children and adults. However, available data raise no new safety concern in patients less than two years of age relative to older patients.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As of April 15, 2016, the sponsor reports that 2867 subjects received Dotarem in 51 phase I to IV clinical studies. Of these subjects, 133 were of ages 2 to 17 years and 52 were children younger than 2 years of age.

7.1.2 Categorization of Adverse Events

The sponsor reports that adverse events (AEs) were characterized by MedDRA version 18.1. In the main DGD-44-063 study, AEs were collected from the time of obtaining informed consent to follow up 7 ± 1 day after Dotarem injection. All post-injection AEs were considered treatment emergent including an AE known to occur any time after injection, an AE with an unknown onset date, and an AE with the same date of onset as injection but unknown time of onset.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For the total n=52 safety population less than two years of age who received a single intravenous injection of Dotarem, the sponsor reports a mean dose of 0.2 mL/kg, mean injection volume of 1.6 mL, and mean injection rate of 1.0 mL/s. Of the 52 exposed subjects, 32 subjects (61.5%) received a dose of >0.1 to ≤0.2 mL/kg and 20 subjects received a dose higher than 0.2 mL/kg. Demographics of the total n=52 safety population were similar to those of the n=45 main study DGD-44-063 as detailed by the sponsor below in Table 8.

Table 8: Demographic characteristics of the safety population less than 2 years of age at inclusion (from Table 4 of Clinical Summary of Safety)

Parameter	Product Administration		
	Not Dosed N=6	Dotarem® N=52	Total N=58
Sex			
n	6	52	58
Male	3 (50.0%)	26 (50.0%)	29 (50.0%)
Female	3 (50.0%)	26 (50.0%)	29 (50.0%)
Age (years)			
n	6	52	58
Mean (SD)	0.64 (0.22)	0.83 (0.60)	0.81 (0.58)
Median	0.6	0.8	0.7
Min; max	0.3; 1.0	0.0; 2.0	0.0; 2.0
Age Distribution			
n	6	52	58
<1 month	0 (0.0%)	5 (9.6%)	5 (8.6%)
≥1 to <24 months	6 (100.0%)	47 (90.4%)	53 (91.4%)
Race			
n	6	45	51
Caucasian	5 (83.3%)	43 (95.6%)	48 (94.1%)
Black	0 (0.0%)	1 (2.2%)	1 (2.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (16.7%)	1 (2.2%)	2 (3.9%)
Missing	0	7	7
Height (cm)			
n	6	52	58
Mean (SD)	69.33 (5.24)	69.13 (11.69)	69.16 (11.17)
Median	69.5	71	70.5
Min; max	62.0; 75.0	47.0; 87.0	47.0; 87.0
Weight (kg)			
n	6	52	58
Mean (SD)	7.77 (1.33)	8.01 (3.04)	7.98 (2.91)
Median	7.7	8.3	8.1
Min; max	6.3; 9.4	2.7; 14.5	2.7; 14.5
Body Mass Index (kg/m²)			
n	6	52	58
Mean (SD)	16.25 (3.01)	16.06 (2.53)	16.08 (2.55)
Median	15.8	16	16
Min; max	13.4; 21.8	11.1; 24.6	11.1; 24.6

7.2.4 Routine Clinical Testing

The clinical testing performed in safety populations in main and supportive studies is summarized in Table 9 below.

Table 9: Clinical studies for safety evaluation of Dotarem in subjects less than 2 years of age (modified from Table 1 of Clinical Summary of Safety)

Study ID/ Year	Area imaged	Dose of Dotarem (mL/kg)	Number of subjects of all ages	Number pf subjects <2 years of age	Clinical monitoring
DGD-44-063/ 2015	Various including CNS	0.2	45	45 (CNS, n=28)	Vitals, lab tests, basic AE
DGD-03-015/ 1988	CNS	0.2	29	3	Lab tests, basic AE
DGD-03-016/ 1988	CNS	0.2	20	2	Basic AE
DGD-03-029/ 1990-1991	CNS	0.2	49	2	Basic AE

For main study DGD-44-063, the sponsor lists safety testing as follows:

- Height and weight at screening visit
- Vital signs (blood pressure and heart rate) at several time points/intervals (at baseline prior to injection, post-injection immediately after MRI, and between 2 and 4 hours and at 24 ± 4 hours post-injection)
- Blood samples for safety laboratory variables centrally analyzed at screening and post-injection at 24 ± 4 hours
    - Hematology: RBC, WBC with differential, platelets, Hct/Hgb, MCV, PT/INR
    - Biochemistry: Na, K, Cl, glucose, BUN, creatinine, total protein, calcium, phosphate, total bilirubin, conjugated bilirubin, AST, ALT, alkaline phosphatase, LDH
- Estimated glomerular filtration rate (eGFR) centrally analyzed at screening and post-injection at 24 ± 4 hours
- Urine samples for safety assessment (urinalysis with dipstick) at screening and post-injection at 24 ± 4 hours
- Tolerance at the injection site over 24 ± 4 hours post-injection.
- Adverse events monitored from the beginning of subject's participation in the study (consent form signature) through follow-up period ending 7 ± 1 days post-injection

Laboratory testing in supporting study DGD-03-015 was performed prior to Dotarem injection as well as 2 hours and 24 hours following injection and included certain hematology parameters (RBC, WBC, platelets, reticulocytes, hemoglobin, PT) and certain biochemical parameters (Na, K, BUN, calcium, total bilirubin, alkaline phosphatase, AST, ALT, GGT, LDH, total iron).

Reviewer comments: 1) In main study DGD-44-063, post-drug creatinine was monitored only 24 hours after dosing, lowering sensitivity for asymptomatic subacute renal toxicity. 2) Because the delay between GBCA dosing and NSF can range up to years (median ~60 days), post-marketing data is most sensitive for detection of NSF. 3) Under-reporting of certain AEs is likely in young pediatric subjects who cannot express the presence of basic symptoms such as nausea, headache, and other types of discomfort or pain.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported by the sponsor in any subjects less than 2 years of age in all clinical studies.

7.3.2 Nonfatal Serious Adverse Events

The sponsor reports three nonfatal serious adverse events (SAEs) (moderate anemia, moderate pyrexia, and mild upper respiratory tract infection) occurring in a single subject aged 1-year on the day after Dotarem administration. None of these SAEs were considered related to Dotarem administration. After review of the sponsor's related narrative account of these SAEs, we agree with this non-causal assessment. All of these SAEs resolved within seven days with treatment. Two additional subjects each experienced one SAE (anemia and thrombocytopenia, respectively) before the administration of Dotarem.

7.3.3 Dropouts and/or Discontinuations

No dropouts or discontinuations associated with adverse effects were noted by the sponsor in any subject less than 2 years of age.

7.3.4 Significant Adverse Events

Only a single AE in pediatric subjects less than 2 years of age was considered related to Dotarem. This 20-month old female subject was imaged for neuroblastoma and

developed a rash of moderate intensity on the same day Dotarem was injected that resolved after five days of medication.

For reference, from the n=2867 overall safety population receiving Dotarem in all clinical studies, 254 (8.9%) subjects experienced at least one post-injection AE with 114 (4.0%) subjects experiencing AEs that were considered related to Dotarem exposure. Rash is included in the sponsor's listing of most common related AEs in the overall safety population as appears in Table 10 below.

Table 10: Incidence of related adverse events in ≥0.2% of all subjects who received Dotarem

Adverse Drug Reaction	% of n=2867
Nausea	0.6%
Headache	0.4%
Injection site pain	0.4%
Injection site coldness	0.2%
Rash	0.2%

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Of the n=52 pediatric subjects less than 2 years of age who received Dotarem, 14 subjects (26.9%) experienced at least one post-injection AE, all of which were mild or moderate in intensity. The most common of these post-injection AEs were pyrexia in 6 subjects (11.5%), vomiting in 2 subjects (3.8%), and leukopenia in 2 subjects (3.8%). All other observed AEs occurred in no more than one patient. The sponsor's complete listing of all AEs reported in the n=52 safety population of subjects less than two years of age appears below in Table 11.

Table 11: Adverse events occurring post-injection of Dotarem in subjects less than 2 years of age (from Table 86 of Integrated Summary of Safety)

System Organ Class Preferred Term	Product Administration	
	Dotarem® N=52[a]	
	N (%) patients	n events
General disorders and administration site conditions	**6 (11.5%)**	**7**
Pyrexia	6 (11.5%)	6
Fatigue	1 (1.9%)	1
Infections and infestations	**6 (11.5%)**	**7**
Bronchitis	1 (1.9%)	1
Infection	1 (1.9%)	1
Nasopharyngitis	1 (1.9%)	1
Rhinitis	1 (1.9%)	1
Tonsillitis	1 (1.9%)	1
Upper respiratory tract infection	1 (1.9%)	1
Urinary tract infection	1 (1.9%)	1
Gastrointestinal disorders	**4 (7.7%)**	**5**
Vomiting	2 (3.8%)	2
Abdominal pain	1 (1.9%)	1
Diarrhoea	1 (1.9%)	1
Nausea	1 (1.9%)	1
Blood and lymphatic system disorders	**2 (3.8%)**	**4**
Leukopenia	2 (3.8%)	2
Anaemia	1 (1.9%)	1
Thrombocytopenia	1 (1.9%)	1
Nervous system disorders	**1 (1.9%)**	**1**
Tremor	1 (1.9%)	1
Product issues	**1 (1.9%)**	**1**
Device difficult to use	1 (1.9%)	1
Respiratory, thoracic and mediastinal disorders	**1 (1.9%)**	**1**
Cough	1 (1.9%)	1
Skin and subcutaneous tissue disorders	**1 (1.9%)**	**1**
Rash	1 (1.9%)	1

7.4.2 Laboratory Findings

No common or unexpected changes in laboratory values related to Dotarem administration were reported by the sponsor.

7.4.3 Vital Signs

In main study DGD-44-063, small mean decreases in systolic blood pressure, diastolic blood pressure, and heart rate were noted immediately following MRI compared to baseline with larger mean increases in these parameters at time points 2 to 4 hours and

24 hours after injection. The sponsor speculates that this trend may be explained by sedation at the time of MRI and subsequent recovery. There was, however, a large range of change in vital signs from baseline to subsequent time points, including subjects with decreased values. Considering the relatively small number of subjects studied and the background variation in vital signs among these subjects, a related safety concern does appear evident.

7.4.4 Electrocardiograms (ECGs)

ECG monitoring was not performed in pediatric subjects less than 2 years of age. The sponsor indicates that no safety signal was noted in ECG data previously collected in pediatric subjects aged 2 years and older.

8 Postmarket Experience

Under the assumption that each vial or pre-filled syringe of Dotarem sold equates to one treatment course, the sponsor estimates roughly (b) (4) treatment courses in patients of all ages, world-wide from 1997 to May 31, 2016. Accurate e data before 1997 are not available according to the sponsor. Approximatel (b) (4) exposures are estimated to have taken place in the United States from the time of approval in 2013 to March 31, 2016. At the previously mentioned Medical Imaging Drugs Advisory Committee held on February 14, 2013, to discuss initial FDA approval of Dotarem, it was estimated that roughly (b) (4) patients under 2 years of age had been exposed to Dotarem worldwide.

Cumulatively, a total of 14 cases with 24 adverse drug reactions (ADRs) were reported in children younger than 2 years of age through post-marketing data sources. The MedDRA system organ class (SOC) and preferred term (PT) for these ADRs as listed by the sponsor appear in Table 12 below.

Table 12: Cumulative summary tabulation of all ADRs reported through post-marketing sources in patients less than 2 years of age (from Appendix 7 of the Post-Marketing Safety Update report dated 8/25/16)

		Children < 2 years		
Primary SOC	**PT**	**All**	**Serious**	**Not Serious**
Cardiac disorders	Tachycardia	**1**	1	
Eye disorders	Eye swelling	**1**	1	
General disorders and administration site conditions	Extravasation	**1**		1
	Injection site induration	**1**		1
	No adverse event	**2**		2
Injury, poisoning and procedural complications	Accidental overdose	**2**		2
	Incorrect route of drug administration	**1**	1	
	Off label use	**1**	1	
	Overdose	**4**	2	2
Investigations	Body temperature increased	**1**	1	
	Heart rate decreased	**1**	1	
Nervous system disorders	Seizure	**1**	1	
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	**1**	1	
	Stridor	**1**	1	
Skin and subcutaneous tissue disorders	Dermatitis allergic	**1**		1
	Erythema	**1**		1
	Rash	**1**	1	
	Urticaria	**2**	1	1
Total		**24**	13	11

For reference, a pharmacovigilance report for the period between November 1, 2012 (b) (4) 15, 2016, was included in this sNDA submission accounting for approximately (b) (4) exposures world-wide in both adults and children including all of the roughly estimated US exposures. Older pharmacovigilance data were previously reported at the time of the initial FDA approval of Dotarem. In general, SOCs encompassing ADRs reported in children younger than 2 years of age also contained a relatively large proportion of the 4743 ADRs reported in the total population between November 1, 2012 and April 15, 2016. For example, the SOC of "skin and subcutaneous tissue disorders" which accounted for 5 of the 24 ADRs (21%) in patients less than 2 years of age was also the most commonly reported SOC in the total population during the reporting period with 1306 of 4743 ADRs (28%). As a notable exception, the "injury, poisoning, and procedural complications" SOC appears to be over represented in patients less than two years of age compared to the total population. Of the 8 ADRs in this SOC in children younger than 2 years of age, 6 cases involved overdose, 4 of which cases had no additional associated AEs. Inference of any age-related increase in propensity of ADRs in this SOC or any other, however, is

difficult given the low number of total ADRs reported in children younger than 2 years of age.

Of additional note, in the total world-wide population during the November 1, 2012 to April 15, 2016 reporting period, 6 deaths in adults were attributed to severe anaphylaxis. No fatalities involving anaphylaxis or any other cause has ever been reported in children of less than 2 years of age. Not including NSF, an additional 13 cases of nephrotoxicity were identified in adults during the reporting period with most confounded by preexisting renal failure, concomitant medications, or a predisposing condition like diabetes. No nephrotoxicity has been reported in children less than 2 years of age. A single SAE of convulsions was reported in pediatric patients younger than 2 years of age but was attributed to inappropriate administration route as Dotarem was injected into the cerebral ventricles despite contraindication for intrathecal exposure.

During the November 1, 2012 and April 15, 2016 period, 9 cases of NSF were reported in the total Dotarem pharmacovigilance population for an all-time cumulative total of 46 NSF cases reported after possible Dotarem administration. The sponsor states that of this cumulative total, Dotarem administration was confirmed in only 20 cases and of these cases, NSF was confirmed in only 7 cases. All 7 of these confirmed NSF cases were confounded with the administration of other GBCAs in addition to Dotarem. Two other cases of reported NSF following known administration of only Dotarem are contested by the sponsor as having inconsistent or insufficient clinical information to confirm the diagnosis of NSF. However, our review of the related narrative histories leads us to conclude that NSF cannot be definitively excluded in these 2 patients with the currently available data. In any event, no NSF cases related to Dotarem or any other GBCA have ever been reported in children less than 2 years of age. For reference, the cumulative number of NSF cases worldwide from any cause is approximately 500, including roughly 10 pediatric patients, all 6 years of age or older (Weller et al., Pediatr Nephrol 2014 29: 1927-1937)

Eight observational post-marketing surveillance studies reported between 1991 and 2013 included 259 patients less than 2 years of age. The sponsor indicates that no AEs were reported in this age group. Within these observational studies, 213 pediatric patients under the age of 2 years were imaged for a CNS indication and were described by the sponsor as evaluable for imaging efficacy. Only two of these studies, DGD-55-001 and DGD-55-002, which had the largest numbers of patients younger than 2 years of age, reported CNS imaging efficacy data specifically for pediatric patients younger than two years of age. Both of these studies, which are discussed individually below, provided supportive CNS imaging efficacy results in the target population through evaluation of post-contrast images alone.

Post-marketing surveillance study DGD-55-001 was conducted in 10 countries outside of the U.S. between 2008 and 2013 and included 85 pediatric patients under the age of 2 years who were referred for CNS MRI studies with Dotarem. Image quality was rated

as “good” or “very good” (4 or 5 on a 5-point scale) in 84 of these 85 patients, presumably by a single site-reader per study. In 83 of 84 of these subjects, diagnosis was rated as “possible” with only 1 subject’s diagnosis rated as “impossible”. This diagnostic rating data were missing for 1 of the 85 subjects who were evaluable for image quality.

Post-marketing surveillance study DGD-55-002 was conducted at a single site in France between 2003 and 2011 and included 85 pediatric patients between 3 days and 18 months of age who were referred for CNS MRI studies with Dotarem. Image quality was rated as “good” or “excellent” (4 or 5 on a 5-point scale) in 83 of these 85 patients, presumably by a single site-reader per study. Of the 85 patients, a diagnosis of “definitely normal” or “definitely abnormal” was made in 83 cases, with an additional 1 case rated as “probably normal”, 1 case rated as “indecisive”, and no cases rated as “probably abnormal”. Additional survey data was collected regarding the impact of MRI images on therapeutic management in the 85 patients, with 45.9% of studies affecting choice of initial treatment, 29.4% of studies resulting in no treatment, 18.8% of studies leading to continuation of current treatment, and 5.9% of studies causing a change in treatment.

9 Appendices

9.1 Literature Review/References

FDA (2017) FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue (accessed 7/27/07)

FDA (2015) FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI) (accessed 7/27/07)

FDA (2013) 2013 Meeting Materials, Medical Imaging Drugs Advisory Committee (accessed 7/27/07)

Fretellier N, et al. (2014) Safety profiles of gadolinium chelates in juvenile rats differ according to the risk of dissociation. Reprod Toxicol 50:171-179.

Hao D, et al. (2012) MRI Contrast Agents: Basic Chemistry and Safety. J Magn Reson Imaging 36:1060-1071.

Maximova N, et al. (2016) Hepatic gadolinium deposition and reversibility after contrast agent-enhanced MR imaging of pediatric hematopoietic stem cell transplant recipients. Radiology 281:418-426.

Mithal L, et al. (2017) Use of gadolinium-based magnetic resonance imaging contrast agents and awareness of brain gadolinium deposition among pediatric providers in North America. Pediatr Radiol 47:657-664.

Pietsch H, et al. (2009) Long-term retention of gadolinium in the skin of rodents following the administration of gadolinium-based contrast agents. Eur Radiol 19:1417-1424.

Robert P, et al. (2015) T1-weighted hypersignal in the deep cerebellar nuclei after repeated administrations of gadolinium-based contrast agents in healthy rats: Difference between linear and macrocyclic agents. Invest Radiol 50:473-480.

Schwartz G, Furth S. (2007) Glomerular filtration rate measurement and estimation in chronic kidney disease. Pediatr Nephrol 22:1839–1848.

Tedeschi E, et al. (2017) Gadolinium retention in the body: what we know and what we can do. Radiol Med 122: 589-600.

Weller A, et al. (2014) Gadolinium and nephrogenic systemic fibrosis: an update. Pediatr Nephrol 29:1927-1937.

9.2 Labeling Recommendations

- Section 1 Indications and Usage and Section 2 Dosage and Administration
  - Add proposed language of “including term neonates”.
- Section 6 Adverse Reactions
  - Update 6.1 Clinical Studies Experience with new safety data from clinical trials for both children and adults
- Section 8 Use in Specific Populations
  - Revise 8.4 Pediatric Use to contain the following:
    - The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg have been established in pediatric patients from birth (term neonates defined as ≥37 weeks amenorrhea) to 17 years of age based on clinical trials conducted with 133 pediatric patients aged 2 years and older and 52 pediatric patients aged from birth to less than 2 years that supported extrapolation from adult data *[see Clinical Studies (14)]*. Adverse reactions in pediatric patients were similar to those reported in adults *[see Adverse Reactions (6.1)]*. No dose adjustment according to age is necessary in pediatric

patients *[See Dosage and Administration (2.1), Pharmacokinetics (12.3)].* The safety of DOTAREM has not been established in preterm neonates.

- No cases of NSF associated with DOTAREM or any other GBCA has been identified in pediatric patients age 6 years and younger [*see Warnings and Precautions (5.1)*]. Normal estimated GFR (eGFR) is approximately 30 mL/minute/1.73m^2 at birth and increases to adult values by age 2 years.

- Section 12 Clinical Pharmacology
  - Add the following heading and paragraph to 12.3 Pharmacokinetics, Special Populations
    - Pediatric population
      The pharmacokinetics of DOTAREM in pediatric patients aged birth (term neonates) to 23 months was investigated in an open label, multicenter study using a population pharmacokinetics approach. A total of 45 subjects (22 males, 23 females) received a single intravenous dose of DOTAREM 0.1 mmol/kg (0.2 mL/kg). Ages ranged from less than one week to 23.8 months (mean 9.9 months) and body weights ranged from 3 to 15 kg (mean 8.1 kg). Individual level of renal maturity in the study population, as expressed by eGFR, ranged between 52 and 217 mL/min/1.73 m^2 with 11 patients having an eGFR below 100 mL/min/1.73 m^2 (range 52 to 95 mL/min/1.73 m^2).

- Section 14 Clinical Studies
  - Add the following heading and paragraph:
    - CNS Imaging in the Sub-population of Pediatric Patients < 2 years old
      A non-randomized study (Study C) with 28 pediatric patients under 2 years of age who were referred for contrast MRI of the CNS supported extrapolation of CNS efficacy findings from adults and older children. CNS lesions were identified in 16 of these 28 patients on paired pre- and post-contrast images compared to 15 patients on pre-contrast images alone. In the 16 patients who had identifiable lesions, reader scores for the co-endpoints of lesion visualization were improved for at least one lesion on paired pre- and post-contrast images compared to pre-contrast images in 8 out of 16 (50%) patients for lesion border delineation, 8 out of 16 (50%) patients for lesion internal morphology, and 14 out of 16 (88%) patients for lesion contrast enhancement.

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this pediatric supplement.

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/s/

AUGUST A HOFLING
07/27/2017

ANTHONY F FOTENOS
07/28/2017