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*APPLICATION NUMBER:*

**204781Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	204,781
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Division / Office	Division of Medical Imaging Products
Reviewer Name(s)	Barbara A. Stinson, DO
Review Completion Date	
Established Name	Gadoterate Meglumine
(Proposed) Trade Name	Dotarem
Therapeutic Class	MRI diagnostic contrast agent
Applicant	Guerbet LLC
Formulation(s)	0.5 mmol Gd/mL
Dosing Regimen	Single use, 0.1 mmol/kg IV
Indication(s)	Dotarem is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonate to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
Intended Population(s)	Adults and pediatric patients from neonates to 17 years of age with known or suspected CNS disease

Template Version: [March 6, 2009](#)

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

Possibly recommended for approval in adults and children ages 2 years and older, pending division concurrence and FDA Advisory Committee meeting. Not recommended for children under age 2 years.

### **1.2 Risk Benefit Assessment**

- The applicant met the primary efficacy endpoints in both pivotal trials (DGD-44-050 and DGD-44-051) however the re-read DGD-44-051 study was not fully representative of the population for the proposed indication.
- The safety profile assessment is limited for most clinical trials including the DGD-3-44 study (re read study DGD-44-051).
- Based on the above, the benefit/risk assessment may favor approval based on results from a single confirmatory pivotal phase 3 trial (DGD-44-050) in combination with a second supportive phase 3 trial (DGD-44-051).

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

- The applicant should continue to participate in the established Global Pharmacovigilance Program (GPV) to ensure that information about all suspected adverse reactions is collected and reported in a global safety database.
- The applicant should ensure enhanced pharmacovigilance and risk minimization for the development of Nephrogenic Systemic Fibrosis (NSF).

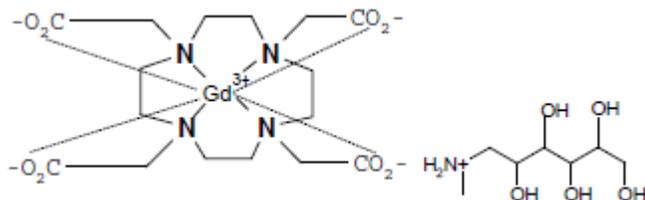
### **1.4 Recommendations for Postmarket Requirements and Commitments**

Pending outcome of the AC meeting, the applicant may be required to conduct studies in children under age 2.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

- Dotarem is a macrocyclic paramagnetic gadolinium (Gd) chelate that causes shortening of relaxation times (T1 and T2) yielding contrast enhancement in magnetic resonance imaging (MRI).
- The non-proprietary (USAN) name is Gadoterate meglumine.
- The proposed trade name is Dotarem.
- The structural formula is reproduced below.



- The molecular formula is  $C_{23}H_{42}O_{13}N_5Gd$ . The relative molecular mass is 753.86 g/mol.
- Chemical class: This product is a new molecular entity (NME). It is an electrically neutral gadolinium complex formed by complexation reaction of gadolinium ions ( $Gd^{3+}$ ) and meglumine, (gadolinium ion linked to a complexing agent or ligand). It is an ionic cyclic (macrocyclic) gadolinium complex.
- Pharmacological class: The product is a gadolinium-based contrast agent (GBCA) that shortens the T1 and T2 relaxation times of hydrogen protons which is seen as an increase of signal intensity in T1 weighted imaging sequences.
- Proposed indication: Dotarem is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonate to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
- Background and rationale: Pathology of the brain such as lesions caused by primary or metastatic brain tumors, stroke, and inflammation disrupt the normal blood brain barrier allowing contrast agents to diffuse into these lesions, which increases their detectability on contrast-enhanced (CE) MR sequences. CE-MR is the clinical “gold standard” for detecting and delineating most intracranial and spinal lesions. The primary objective of the two phase 3 pivotal studies that are presented in this NDA was to demonstrate superiority of combined contrast enhanced/unenhanced MRI versus unenhanced MRI for structural characteristics

of CNS lesions (contrast enhancement, lesion border delineation, lesion internal morphology) to provide information for diagnosis and clinical management.

- The proposed dose is 0.1 mmol/kg (0.2 mL/kg) body weight to be administered as an intravenous bolus injection manually or by power injector at a flow rate of approximately 2mL/sec for adults and 1-2 mL/sec for children followed by a normal saline flush. It is distributed exclusively within the extracellular fluid and eliminated quickly via the renal system, without any metabolism.
- Gadoterate meglumine, the active pharmaceutical ingredient, is formed in situ as part of the drug product manufacturing process. (b) (4)
- Dotarem will be offered as single dose glass vials, single dose pre-filled glass syringes, and pharmacy bulk pack as a glass vial.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are six extracellular MRI contrast agents in the US approved for use in MRI of the central nervous system (CNS). These have the following CNS and non-CNS indications according to their respective labels.

- **Magnevist** is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the brain, spine and associated tissues as well as visualization of lesions with abnormal vascularity of the head and neck and the body (excluding the heart).
- **Omniscan** is indicated for IV use in MRI to visualize lesions with abnormal vascularity in the brain, spine and associated tissues. It is also indicated for IV administration to facilitate the visualization of lesions with abnormal vascularity within the thoracic (non-cardiac), abdominal, pelvic cavities, and the retroperitoneal space. [...Pediatric patients 2-16 years...CNS]
- **Multihance** is indicated for IV use in MRI of the CNS in adults and children over 2 years of age to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues.
- **Optimark** is indicated for use in MRI in patients with abnormal blood brain barrier or abnormal vascularity in the brain, spine and associated tissues. It is also indicated for use with MRI to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography (CT).
- **Prohance** is indicated for use in MRI in adults and children over 2 years of age to visualize lesions with abnormal vascularity in the brain, spine, and associated tissues as well as for use in adults to visualize lesions of the head and neck.

- **Gadavist** is indicated for diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system (CNS)

Of these agents, Omniscan, Magnevist, Prohance, Multihance, and Gadavist are approved for use in pediatric patients over age 2.

Prohance and Gadavist are both macrocyclic gadolinium-based contrast agents that are approved in the US.

There are two additional US approved gadolinium based contrast agents, Eovist and Ablavar, not approved for CNS indications.

The other widely used imaging modality for diagnosis of CNS lesions in the brain for the intended population is contrast-enhanced computed tomography. This modality provides limited evaluation of some structures.

### **2.3 Availability of Proposed Active Ingredient in the United States**

The drug product is a new molecular entity and is not currently marketed in this country. Manufacture and testing is done at two production sites: (b) (4)

### **2.4 Important Safety Issues With Consideration to Related Drugs**

In 2006, the Agency issued a Public Health Advisory notice and recommended that the manufacturers of gadolinium containing products send a Dear Healthcare Provider letter regarding the potential development of Nephrogenic Systemic Fibrosis (NSF) that has been associated with gadolinium containing contrast agents when used in patients with severely impaired renal function ( $GFR < 30 \text{ mL/min/1.73 m}^2$ ). Additionally, class labeling changes for these products included the addition of a black box warning and changes to the Warnings section of the label.

Sponsors are required to report all cases of NSF to the Agency on a quarterly basis.

The FDA recently required that some gadolinium-based contrast agents carry new warnings on their labels in addition to the already required black box warning. Magnevist, Omniscan, and Optimark are now required to be described as inappropriate for use among patients with acute kidney injury or chronic severe kidney disease.

In addition to NSF, the other major safety issues concerning this class of drugs involve hypersensitivity reactions and a risk of acute kidney injury usually in a setting of pre-existing kidney disease.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

IND 65,041 for Dotarem (gadoterate meglumine) was originally submitted by Guerbet to the FDA on June 12, 2002.

In July, 1999, Guerbet met with FDA to discuss CMC issues and obtain guidance on the sterilization validation program and on the stability program to be followed. At that time, the FDA indicated to Guerbet that the API was gadoterate meglumine (and not gadoteric acid) and requested a separate reference standard. Subsequently, Guerbet changed its industrial strategy and has also changed its planned US manufacturing sites.

A pre-IND meeting to discuss future filing was held on September 21, 2000 followed by an IND submission on June 12, 2002. In early 2003, Guerbet discussed CMC issues with the FDA via three teleconferences. This resulted in additional CMC changes leading to changes in industrial strategy and subsequently, changes in planned manufacturing sites for the US market.

On September 9, 2009, Guerbet presented the pivotal CNS study DGD-44-050 to the FDA to be conducted under a Special Protocol Assessment (SPA) and proposed a re-read of the images from the failed DGD-03-44 CNS study as the second study. The FDA agreed that this was acceptable following revision of the SPA. The protocol design, statistical analysis plan, and blinded evaluation charter were rewritten and submitted to the FDA on June 11, 2010, with the SPA concurrence on July 29, 2010.

The nonclinical studies and data were updated on April 22, 2010 following an FDA request for information.

In April and July, 2010, additional meetings were held between the FDA and Guerbet to discuss and update CMC strategy necessary for a successful marketing application which was followed by additional correspondence also regarding CMC strategy in May and June, 2012.

The pre-NDA meeting between Guerbet and the Agency was held on June 12, 2012. The FDA agreed that Guerbet's proposed strategy for the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) was appropriate and that a separate CMC meeting was not necessary. Guerbet confirmed that a pediatric

indication (2 to 17 years) would be sought in the NDA. The possibility of an indication for the 0-23 month age group was discussed.

## 2.6 Other Relevant Background Information

Dotarem was first approved in France in 1989. It is currently approved for the various uses in 70 countries (in Japan, the drug is marketed as Magnescope). In addition to approval for intracranial and spinal MRI, Dotarem is approved for contrast-enhanced MRI of the whole body as well as for contrast-enhanced magnetic resonance angiography (MRA). In various countries, Dotarem is approved for use in pediatrics from neonates to 17 years of age (from age 2 to 17 in UK and Spain). The standard dose throughout the world is 0,1 mmol/kg for CNS, body, and MRA imaging with approval in some countries for an additional 0.2 mmol/kg dose (total 0.3 mmol/kg) for CNS study to increase the diagnostic accuracy of the exam.

Until recently, Dotarem has not been studied in the United States. At this time, in addition to the current application for CNS MRI indication, Guerbet is performing clinical trials in US under Special Protocol Assessment (SPA) (b) (4)

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

DSI was consulted regarding site visits for this NDA. Study -051 was a blinded re-read of the original images from a 2003 phase 3 trial. 8/9 of the clinical sites were located in France. 7 sites enrolled 20 subjects or less. Both sites for inspection were selected from the pivotal trial DGD-44-050 based on the study protocol (conducted under US FDA SPA agreement), date of the study (recent versus 2003 for the -050 trial), and the number and location of sites (53 versus 9 sites and multiple US as well as global locations versus the -050 study with 8/9 sites in France). As indicated in Table 1, one of the two sites selected was a site with the greatest number of treatment emergent (adverse) events and protocol violations given the number of subjects enrolled at the site. The second site was placed on the inspection site list based on the Applicant's request for a pediatric indication with this pediatric hospital enrolling about 20% of the pediatric subjects in the -050 trial. The core laboratory for the independent blinded read

of the images was also recommended for inspection based on the importance of the blinded read results.

Table 1 lists the sites suggested for inspection and the rationale for the recommendation.

**Table 1: Inspection Sites (Pivotal Studies DGD-44-050 and DGD-044-051, Core Lab, Study Files)**

Site # (Name and Address) Chief Investigator	Protocol #	Number of Subjects	Indication
0719 Dr. Delilah Burrowes Children’s Memorial Hospital Department of Medical Imaging 2300 Children’s Plaza Mailbox 9 Chicago, Illinois 60614 Phone: 773-880-4502 Fax: 773-880-3517 Email: dburrowes@childrensmemorial.org	DGD-44-050	7	Applicant is seeking a pediatric indication, need to ensure acceptability of clinical data; number of AEs and protocol violations may be large compared to number of subjects; need to characterize these for a pediatric population
0702 Dr. Gregory Boys Clinical Trials of Texas, Inc. 7940 Floyd Curl Drive Suite 700 San Antonio, Texas 78229 Phone: 210-949-0122 Fax: 210-949-0181 Email: ctt@cttexas.com	DGD-44-050	18	Relatively large numbers of adverse events and protocol violations for study population size as compared to other sites ( 18 subjects with 16 AEs and 22 protocol violations)

(b) (4)

(b) (4)

The Guerbet clinical department in Paris, France holds the trial master file for the two pivotal studies and for all other studies included in the NDA.

Guerbet which is the site that maintains study files will not be inspected by the Compliance Division. Preliminary results of inspections of the first clinical site and the linked read facility have been reported as no action indicated (no action indicated). Results from Dr. Boys' facility are pending.

### **3.2 Compliance with Good Clinical Practices**

The pivotal studies were performed in accordance with acceptable clinical standards, e.g. patients were referred for an MRI contrast-enhanced exam of the CNS based on at least one highly suspected or known CNS lesion (DGD-44-050 or -050) or having lesion or highly suspect for lesion based on previous CT or MR imaging (DGD-44-051 or -051). All subjects were required to sign an informed consent statement. For both studies, there were protocol deviations for about 1/3 of subjects. According to the Applicant and subject to inspections, as above, the majority of the major protocol deviations for the -050 study related to dosing with most minor deviations due to timing. For the -051 study, most of the major protocol deviations were related to biopsy and most of the minor deviations related to timing.

### **3.3 Financial Disclosures**

Guerbet submitted a list of all clinical investigators who participated in the clinical studies. One of the principal investigators for study DGD-44-050 at (b) (6) noted that he had disclosable financial arrangements and interests which consisted of payments for additional grant research since the time of the study. At the time the investigator was chosen, the financial arrangements had not reached the minimum requirement for payments of other sorts with the payments that were disclosed being noted at the end of study enrollment. Guerbet monitored and audited the site with findings of no major protocol violations and no findings to require any specific action from Guerbet. The potential bias based on the database presented is felt by this reviewer to be extremely small.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Dotarem is a stable gadolinium complex. It is ionic and has a macrocyclic configuration. The active ingredient is Gd-DOTA or gadoteric acid which cannot be isolated as such. The drug substance, gadoterate meglumine, is formed

(b) (4)

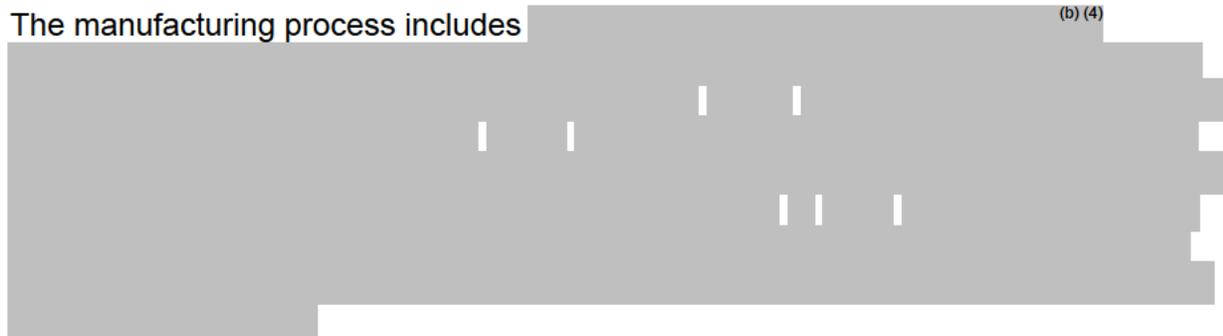


(b) (4)

Synthesis is robust and well defined and the material is well characterized. It is formulated as an 0.5 M formulation similar to other approved agents.

The manufacturing process includes

(b) (4)



Drug product specifications, (identification, physical qualities, assay, and impurities), are adequate to describe and control quality attributes.

It will be marketed as single dose glass vials, single dose glass syringes, and pharmacy bulk pack in a glass. All container closure components meet USP requirements. Stability studies currently support a 18 month expiry for all dosage forms. The proposed shelf life by the applicant is (b) (4)

Methods validation is suitable for all specifications and is similar to approved agents.

CMC tentative recommendation is for approval.

## 4.2 Clinical Microbiology

The drug substance is a sterile, non-preserved solution for injection in single dose containers. It will be supplied in 3 single dose glass vial configurations, 3 single dose clear pre-filled syringe configurations, and 1 clear glass 100 mL vial pharmacy bulk pack configuration. The drug product is (b) (4). The NDA contained validation reports for sterility and bacterial endotoxins. Container closure studies support the proposed configurations. Micro recommendation is for approval pending satisfactory consult results from CDRH regarding the container closure system which is classified as a combination product.

## 4.3 Preclinical Pharmacology/Toxicology

According to the Applicant, safety pharmacology studies were not performed in compliance with Good Laboratory Practices (GLP) except for additional studies which were requested by the FDA in the year 2000. Results of safety pharmacology studies performed in dogs showed moderate and transient effects on cardiovascular and hemodynamic patterns with effects attributed mostly to the osmolality of the injected solution and to the high injected volume. No adverse effects of Dotarem were seen on the ECG in these dogs with no effects on cardiac action potential in dog Purkinje fibers. In a sensitized model in rabbits anesthetized with alpha-chloralose and pre-treated with methoxamine, Dotarem induced an increase in heart rate with a secondary increase in arterial blood pressure without alteration of ECG, in particular without alteration in cardiac conduction times, (QT/QTc interval).

Renal function studies in anesthetized dogs showed moderate and transient increases in renal blood flow, urine output, and urea and creatinine excretion. In a glycerol-induced renal failure model in rats, Dotarem did not influence renal functional

impairment. In an L-Name pretreated rat sensitized model, Dotarem exhibited a better renal tolerance than Magnevist.

For CNS testing in mice, the only notable effect induced by Dotarem was a minor pro-convulsant effect when administered i.v at high dose levels. For rats, this same effect was noted when Dotarem was administered via an intracisternal route. Dotarem does not cross an intact blood brain barrier.

For *in vitro* studies of other systems/functions it was noted that Dotarem induced a decrease in hemolytic activity of the complement and of C3a production. There was no histamine and serotonin release from rat peritoneal mast cells exposed to Dotarem. There was a moderate inhibition of some calcium-dependent enzyme activities *in vitro* at concentrations that could be achieved *in vivo* which, for most cases, was less than for Magnevist. There were no hemolytic effects on rabbit and human blood while high concentrations did induce hemolysis and decrease deformability with rat blood at high concentrations. Dotarem showed a slight anticoagulant effect and a partial inhibition of platelet aggregation.

All pivotal toxicology studies were GLP compliant. Two single dose toxicity studies in mice and two in rats were not GLP-compliant and are considered as supportive studies. The Applicant performed expanded single dose toxicity studies in rats and dogs by intravenous route. No juvenile studies were performed for potential toxicity. Non-clinical toxicology studies performed in rats and dogs showed low acute toxicity with no mortality at dose levels adjusted for body surface area representing 24 and 40 times the intended diagnostic dose respectively. Depressive central clinical signs at the lowest dose and a dose-related vacuolated cortical tubular epithelium, in kidneys (partially reversible) were noted in rats. Repeat dose toxicity studies were performed in rats and dogs after administration of Dotarem for 4 weeks with no major toxicity noted. As was noted for the single dose studies, the main findings were vacuolated cortical tubular epithelium in the kidneys which was generally associated with increased kidney weight and with partial reversibility of the treatment changes noted after the 4 week treatment period. For renal function, Dotarem induced minor glomerular and tubular dysfunctions when given at high doses. It was well tolerated in animal models with renal injuries. At the highest dose levels, vacuolated urothelium, hepatocytes, and histiocytes were noted with these lesions partially reversible after a 4 week treatment free period. Hematological and biochemical parameters were slightly but significantly modified at very high doses with effects totally reversible at the end of a 13 week treatment period. Dotarem was not genotoxic and showed no reproductive and developmental toxicity in rats and rabbits. It did not induce testicular damages or impair male fertility. Dotarem induced no mutagenic or clastogenic effect and no chromosomal aberration in either the *in vitro* or *in vivo* tests. There were no effects on fertility and reproductive performances up to a dose of 10 mmol/kg/day in rats. There was no evidence of embryotoxicity, fetotoxicity, or teratogenicity in doses up to 10 and 3 mmol/kg in rats and rabbits respectively. In rabbits there was maternal toxicity as 7 mmol/kg with a high mortality

rate and thus it was not possible to study embryotoxicity at this dose. Subcutaneous and intravenous administration in rats and intravenous, intra-arterial, and perivenous administration in rabbits were well tolerated locally. There was no immunogenic potential with no antigenicity induced and no active systemic anaphylactic reactions after administration to guinea pigs. Dotarem solution spiked with with impurity (b) (4) did not induce additional toxicity and it was not mutagenic.

The Applicant conducted pre clinical PK studies to establish the ADME Bioanalyses profile of Dotarem (Gd-DOTA) after single and repeated intravenous administration in different animal species, to evaluate under these experimental conditions the body retention of gadolinium, and to compare Dotarem to Magnevist,(Gd-DTPA). Mice, rats, rabbits, and dogs were studied using mainly intravenous administration. Total gadolinium was measured in tissues and biological samples by Atomic Emission Spectrometry (AES). Animals were administered the same formulation as in clinical trials which is the same formulation that is marketed. PK studies in rats, rabbits, and dogs showed that Dotarem behaved similarly to other agents in the class with rapid distribution to the vascular and extra cellular space, short elimination half life (about 1 hour in various animal species studied), no protein binding, no metabolism, and a rapid and massive elimination. PK studies after single intravenous administration showed low concentrations of Gd-DOTA in many organs, the highest concentrations being in the kidneys and bones. Dotarem was distributed throughout the whole body without restriction except that it did not cross the blood brain barrier. It was concentrated in the kidney (for excretion). Biliary excretion was negligible. Pre clinical studies showed that a negligible amount crossed the placenta and was excreted into milk. Oral absorption was low. The potential toxic effects linked to the presence of gadolinium in milk were not further investigated based on the extremely low dose (0.016% of dose administered 48 hours after injection) and that very small amounts of gadolinium cross the gastrointestinal barrier after oral administration. The pharmacokinetics were similar to Gd-DTPA, (Magnevist).

The applicant performed a comparative study of the excretion of Dotarem and Magnevist administered intravenously in anesthetized rats with renal failure. A study in these rats showed that the plasma half life of Dotarem increased from approximately 0.5 hours in the normal rat to approximately 12 hours in the rats with renal failure and that biliary excretion was multiplied by a factor of 5. Peritoneal dialysis was effective with approximately 30% of the injected dose eliminated in 4 hours reducing the plasma half life to approximately 4 hours. Results confirmed the massive and rapid excretion of gadolinium in normal animals with about 90% of the dose recovered in urine over 4 hours following treatment. Biliary excretion of gadolinium was low but increased markedly in animals with renal failure. Plasma levels of gadolinium were higher in animals with renal failure compared to normal animals and there was a slower decrease in plasma levels over time in the renal failure animals. Following dialysis, gadolinium was detected in the dialysate of renal failure animals and the amount of gadolinium in the plasma of renal failure animals was greater in the animals that did not undergo

dialysis. In comparison to Magnevist, animals that had renal failure and that received Dotarem had a slightly greater increase in biliary excretion of Dotarem in the animals that underwent dialysis.

The PK drug interaction potential was not assessed.

The pre-clinical considerations for nephrogenic systemic fibrosis, (NSF), presented by the Applicant were reviewed. Based on toxicology studies performed on various gadolinium agents, the macrocyclic drug complexes such as Dotarem have an improved toxicity profile when compared to the linear agents. The applicant (published by Fretellier et al) has conducted non clinical studies in rats that were renally impaired by subtotal nephrectomy and found no induction of macroscopic skin lesions with either Dotarem or gadodiamide (Omniscan) in contrast with non-formulated gadodiamide (Omniscan without the free ligand caldiumide). The non formulated product was also associated with a high systemic toxicity and histopathological skin lesions. This same study cites almost no pathological lesions in the Dotarem group while degradation of collagen fibers was observed in the dermis of Omniscan treated rats. Another study performed by the Applicant noted a higher total gadolinium concentration in the skin and the femur of Omniscan and non-formulated gadodiamide treated rats than in Dotarem treated rats. *In vivo* dissociation and the presence of dissociated  $Gd^{+3}$  in a soluble form were seen in the skin and femur of renally impaired rats receiving Omniscan and gadodiamide while Dotarem remained stable over the same study period. In a third study that was performed in renally impaired rats, Haylor reported higher total gadolinium concentration in various tissues of rats receiving Omniscan compared to Dotarem. Haylor noted the dermal retention to be within collagen fibrils in the dermis. An *in vitro* study showed that both Gd-EDTA and Omniscan stimulated human fibroblast viability and fibroblast collagen production and suggested that the collagen production was secondary to an initial stimulatory effect on fibroblast viability. In this study, Dotarem had little effect on fibroblasts. Fretellier et al investigated hyperphosphatemia in renally impaired rats and showed that hyperphosphatemia sensitizes the renally impaired rats to the profibrotic effects of Omniscan but with no effects for Dotarem or other categories of gadolinium chelates. These same animals had gradual *in vivo* dissociation of Omniscan whereas other gadolinium chelates remained stable. The NDA has links to various references that discuss NSF including statements regarding NSF for various gadolinium agents with consideration to NSF occurrence associated with gadolinium deposition and renal insufficiency. The review noted the propensity for gadolinium deposition in skin and other tissues and reviewed skin gadolinium levels 35 and 364 days after IV administration. At both time periods, skin deposition was greatest for the non-ionic linear GBCAs, followed by the ionic, linear GBCAs, with relatively small amounts noted for the macrocyclic agents. At day 364, skin deposition for the macrocyclic agents was similar to untreated control or to saline, (slightly higher).

Regarding NSF, the applicant cited, among other studies, a recent study describing the clinical, biological and skin histopathological effects of ionic macrocyclic and non-ionic linear gadolinium chelates in renally-impaired rat model of NSF, (Fretellier et al, 2012).

No juvenile animal studies were submitted. Preliminary conclusions based on studies of NSF provided by the sponsor were as follows:

1. There is a potential for gadolinium skin deposition in all evaluated gadolinium products.
2. The propensity for skin deposition seems to be higher with linear gadolinium agents.
3. Accumulation of gadolinium in skin and tissues appears to be higher in nephrectomized rats used as a model for renal impairment.
4. Omniscan appears to be the “worst” offender.

At the time of the Applicant Orientation Meeting, it was not clear which pre clinical studies had been conducted by the Applicant as versus studies cited in the literature or studies conducted by other companies. The extent of the studies, such as the genotoxicity studies and whether there were controls for the studies was also not clear. The Pharm/Tox review summarized and concluded that the safety and toxicity profiles of Dotarem appeared adequate but that studies in juvenile animals were lacking. During the course of the NDA review, the applicant submitted a proposed P/T study to the FDA.

*Reviewer’s Comments:*

- 1. It is not clear which pre clinical studies had been conducted by the Applicant as versus studies cited in the literature or studies conducted by other companies.*
- 2. The extent of the studies, such as the genotoxicity studies and whether there were controls for the studies is also not clear.*
- 3. Studies in juvenile animals are lacking.*

#### **4.4 Clinical Pharmacology**

The applicant conducted 4 PK studies in adult humans comprised of 1 study to evaluate safety and PK after single administration of Dotarem, 1 study to evaluate safety and PK of Dotarem after single and triple dose injections, 1 study to evaluate safety and PK of Dotarem in normal subjects and in subjects with renal failure, and one study to evaluate safety and PK (in particular electrocardiographic safety) in subjects receiving a triple dose of Dotarem. PK studies evaluated the effects of endogenous factors such as age

and body weight based on pooled data consisting of all phase 1 studies in healthy adults. No studies were conducted to assess placebo versus Dotarem.

Study DGD 3-6 was conducted in 6 healthy male volunteers ages 20-29 for PK determination using blood, urine, and feces collections up to 48 hours post dose. Vital signs were recorded during the course of the study. The data were consistent with a two compartment model in which the intravenously administered dose was rapidly distributed between a central and peripheral compartment (passive extravascular diffusion in the interstitial space) and was then eliminated primarily in urine by glomerular filtration with a small amount of fecal excretion (less than 0.002%). The volume of distribution at equilibrium suggested test material distribution in extracellular water. Two subjects noted mild adverse effects described in the study report as irritation of the eyes and throat with slight edema of one eyelid for one subject and transient sensation of suffocation for another subject.

The primary objective of study DGD-48 was to calculate PK parameters of Dotarem after 0.1 mmol/kg injection in a group of healthy volunteers ages 18-45 and to calculate similar parameters in a second group that received a second injection of 0.2 mmol/kg after 20 minutes. Follow up was up to 48 hours. In the first group, there were differences in drug distribution attributed to higher body weight in men. Apart from this, the results of the study showed that exposure is dose proportional. 73-85% of the dose was recovered in urine over the 48 hour interval. Laboratory tests and vital signs were unremarkable. Four AEs were noted.

A thorough QT study was performed including PK. 40 subjects received an 0.1 mmol/kg dose of Dotarem followed by a second dose of 0.2 mmol/kg 20 minutes later. Eleven ECGs were recorded for each subject for each period. The central tendency analysis on absolute values and changes from baseline value of QT and/or QTc measured at numerous time points during the study showed no difference between active treatment and placebo. Results of the statistical analysis showed that Dotarem administration did not result in prolongation of QT or QTc intervals by more than 5 ms compared to placebo when analyzing maximal increases. Analysis of the AUC for both treatments confirmed this. Results of the analysis of outliers confirmed this. No QT or QTc value above 480 ms and no QT or QTc increase above 60 ms was observed after either treatment. No increase in QT or QTcF greater than 30 ms was observed after Dotarem administration. 6 patients had QT and QTc values greater than 450 ms, 3 under both treatments and 3 under Dotarem only. These occurred as isolated occurrences. 7 patients (4 under placebo, 3 under Dotarem) had QTcB increases above 30 ms. No clinically significant abnormalities were noted on other ECG parameters, (heart rate, Pr, QRS, T and U waves, 24 hour Holter recordings). 7 of the 40 patients reported adverse events that were mild to moderate in intensity, most frequently headache. There were no clinically significant abnormalities in the laboratory safety parameters or in vital signs. No definite cardiac signals were noted after review by the QTc team.

Study DGD-3-28 was a study in patients with chronic renal failure with comparison control to a population of healthy subjects. 12 patients were equally distributed in three groups of different stages of renal impairment or into a normal group as defined by serum creatinine clearance: (1) moderate impairment of creatinine clearance, (clearance <60 and >30 mL/min); (2) severe impairment (clearance <30 mL/min and > 10 mL/min) and; (3) normal renal function. Patients received an 0.1 mmol/kg bw dose of Dotarem. Blood and urine PK parameters were evaluated before and after injection for 24 hours in the healthy subjects, for 48 hours in subjects with moderate impairment, and for 72 hours in subjects with severe impairment. The mean half life was 1.62 hours in normal subjects, 5.05 hours in subjects with moderate renal failure, and 13.9 hours in subjects with severe renal failure. Laboratory safety parameters were reported as satisfactory with no AEs reported. The overall conclusion was that increasing renal impairment was associated with decreased clearance of Dotarem.

No studies were conducted to assess placebo versus Dotarem.

There was no pediatric PK study.

The applicant did not conduct any dose ranging studies.

The conclusion of the Clin/Pharm reviewer was that Dotarem is similar to other GBCAs and that the PK is linear however PK studies need to be conducted in the population under age 2 to establish parameters in this age group. Additionally, dose response exposure and urinary excretion of gadolinium in children may need to be studied.

*Reviewer's Comments:*

- 1. No studies were conducted to assess placebo versus Dotarem.*
- 2. There was no pediatric PK study.*
- 3. The applicant did not conduct any dose ranging studies.*

#### 4.4.1 Mechanism of Action

Dotarem is an extracellular MRI contrast agent that produces contrast enhancement, (CE). The gadolinium ion has paramagnetic properties due to its 7 unpaired electrons leading to a high magnetic moment and very labile water coordination properties. When

placed in a magnetic field, gadolinium enhances the MR signal and produces the contrast enhancement (increased signal intensity) by shortening T1 and T2 relaxation times of water protons in blood and tissues. Increased signal intensity is seen in T1 weighted sequences. Reduced signal intensity is seen in T2 weighted sequences. For gadolinium chelates, their effects on proton relaxation times and consequently on the MR signal and the contrast obtained are characterized by the relaxivity of the contrast agent molecule. Visualization of normal and pathological tissue depends in part on the variations in the radiofrequency signal intensity that occur with differences in proton density, differences in the T1 relaxation times, and differences in the T2 relaxation times.

#### 4.4.2 Pharmacodynamics

Dotarem leads to a shortening of the relaxation times of protons in plasma, referred to as relaxivity. Both T1 and T2 relaxivity occur. Relaxivity values are similar across the spectrum of magnetic field strengths used in clinical MRI. The applicant did not conduct any pharmacodynamic drug interaction studies based on the single dose use and low interaction potential reported in previously published studies.

#### 4.4.3 Pharmacokinetics

PK is similar across species and has been studied as a single-dose in rat, rabbit, dog, and monkey. There is rapid distribution of gadobutrol in the extracellular space after injection. The PK is linear. The  $t_{1/2}$  (elimination from plasma) of a clinical dose in humans is 1.82 hours. The AUC (area under the curve), increases dose-proportionally. It has low protein binding with >95% noted as unbound. It is not metabolized. Excretion is rapid with >90% of excretion noted to be renal and minimal fecal excretion. There is no accumulation after repeat dosing.

CNS PK studies showed that Dotarem does not cross an intact blood brain barrier.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

In addition to two phase-3 studies submitted in support of the proposed indication, the Applicant conducted 21 clinical trials which are supportive of the CNS indication. There were no phase 1 clinical trials (i.e. no PK or dose ranging studies) conducted for the

indication. There were 11 phase 2 studies which included 2 studies in children (neonates through age 17), 9 phase 3 studies one of which was the original study that re-read as a “pivotal” trial, and there were 2 phase 4 studies with one of these studies conducted in children ages neonate through 17 years. 7 subjects in these trials were 0-23 months. Overall, there were a total of 130 subjects ages 1.2 months to 17 years in the pediatric trials. 36 pediatric subjects ages 2-17 were enrolled in the pivotal DGD-44-050 trial. Table 2 below is an overview of the CNS pivotal trials and supportive studies.

**Table 2: Overview of Clinical Studies For The CNS Indication**

<b>Study # Study year Blinded reading (BR) Study sites location(s )</b>	<b>Subject Age Range (yrs) # Subjects enrolled # Treated (Study Drug)</b>	<b>Study Phase/Design Type of control</b>	<b>Study and control drugs Dosage and regimen (route: Intravenous)</b>	<b>Study Indication and Evaluation Criteria</b>
<b>Study reports and related information of controlled clinical studies pertinent to the claimed indication</b>				
DGD-44-050 2010 BR US, Latin America, Europe, South Korea	3-95 402 278	Phase 3 Randomized Double Blind Multicenter Comparative (unenhanced images vs unenhanced + contrasted images)	Dotarem 0.1 mmol/kg (278) Magnevist 0.1 mmol/kg (117)	Detection and visualization of CNS lesions Lesion visualization characterization Safety- ECG, BP, HR, Lab tests
DGD-44-051 2010 BR France, Germany	18-79 151 150	Phase 3 Not randomized Open label Multicenter Comparative	Dotarem 0.1 mmol/kg	Detection and visualization of CNS lesions Lesion visualization characterization Safety-Vital signs
<b>Study Reports and related information of randomized studies pertinent to the claimed indication</b>				
DGD-3-31 1988 France,	18-79 299 149	Phase 3/4 Randomized Double blind	Dotarem 0.1 mmol/kg (149) Magnevist 0.1	Diagnostic confidence-various neurological

Belgium, Switzerland		Multicenter Comparative Parallel group	mmol/kg (149)	conditions Safety-no labs or discomfort assessment
DGD-3-17 1988 France	18-77 20 10	Phase 2 Randomized Double blind Multicenter Comparative Parallel group	Dotarem 0.1 mmol/kg (20) Magnevist 0.1 mmol/kg (20)	Diagnostic confidence-various neurological conditions Safety-Lab tests
<b>Study Reports and related information of non-randomized studies pertinent to the claimed indication</b>				
DGD-3-40 1999 France, Switzerland, Belgium, Luxem- bourg	54-88 59 59	Phase 4 Non-randomized Open label Multicenter Comparative	Dotarem 0.2 mmol/kg	Double dose perfusion MRI Functional MR imaging in Alzheimer's Disease Image quality Safety-no labs or discomfort assessment
DGD-3-14 1987 France	18-70 55 55	Phase 3 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-discomfort assessment
DGD-3-08 1987 France	20-72 54 54	Phase 3 Non-randomized Open label Single center Comparative(CT)	Dotarem 0.1 mmol/kg	Diagnostic contribution Safety-discomfort assessment
DGD-3-23 1988 France	18-69 50 50	Phase 3 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-none noted
DGD-3-21 1988 France	16-80 2 children 50 50	Phase 3 Non-randomized Open label Single center Comparative(CT)	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-discomfort assessment
DGD-3-20 1988	24-72 48	Phase 3 Non-randomized	Dotarem 0.1 mmol/kg	Diagnostic contribution and

France	48	Open label Single center Comparative(CT)		therapeutic management; neurophthalmic disease and (b) (4) Safety-discomfort assessment
DGD-3-33 1994 France, Belgium	25-81 65 65	Phase 3 Non-randomized Open label Single center Comparative	Dotarem 0.3 mmol/kg (0.1 + 0.2)	Brain metastases for detection and delineation Safety-none noted
DGD-3-34 1994 France, Switzerland	20-82 45 45	Phase 3 Non-randomized Open label Single center Comparative	Dotarem 0.3 mmol/kg (0.1 + 0.2)	Brain metastases for detection and delineation Safety-lab tests
DGD-3-44 2003 BR France, Switzerland, Germany	18-79 151 150	Phase 3 Non randomized Open label Multicenter Comparative	Dotarem 0.1 mmol/kg	Detection and visualization of CNS lesions Lesion visualization characterization Re-read for NDA Safety-vital signs, discomfort assessment
DGD-3-7 1987 France	18-82 56 56	Phase 2 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-discomfort assessment
DGD-3-11 1987 France	24-76 19 19	Phase 2 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-EEG, lab test
DGD-3-04 1987 France	17-72 20 20	Phase 2 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-Lab tests, discomfort assessment

DGD-3-01 1987 France	21-66 10 10	Phase 2 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-Lab tests, discomfort assessment
DGD-3-12 1987 France	18-76 50 50	Phase 2 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-discomfort assessment
DGD-3-05 1987 Belgium	12-74 1 child 10 10	Phase 2 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-lab tests, discomfort assessment
DGD-3-09 1988 Belgium	27-76 22 22	Phase 2 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-lab tests
DGD-3-03 1988 France	21-75 30 30	Phase 2 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Diagnostic contribution and therapeutic management Safety-lab tests, discomfort assessment
DGD-3-29 1991 Children France	1-17 50 50	Phase 4 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Visualization and therapeutic approach Safety-none noted
DGD-3-15 1988 Children France	0.04-17 29 29	Phase 2 Non-randomized Open label Single center Comparative	Dotarem 0.1 mmol/kg	Visualization and therapeutic approach Safety-20/29 lab tests
DGD-3-16	0.5-17	Phase 2	Dotarem 0.1	Visualization and

1988 Children France	20 20	Non-randomized Open label Single center Comparative	mmol/kg	therapeutic approach Safety-none noted
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The total number of clinical trial studies conducted by Guerbet using Dotarem including additional whole body studies (9) and MRA studies (13) include 6 phase 4 studies, 27 phase 3 studies, 12 phase 2 studies, and 4 PK studies with 1 of the PK studies considered to be a phase 2 study. This latter study, a thorough QT/QT<sub>c</sub> study, was conducted using a triple dose of Dotarem. Included in the listing of clinical studies are two special population studies, one of which was a PK study in patients with renal impairment and a phase 3 study in patients with chronic renal failure.

Table 3 below presents an overview of clinical studies for Dotarem for all indications. An efficacy summary and a safety summary for each study are included in the table. As the Applicant has noted all CNS studies as supportive studies, the synopses for these studies are more detailed. Further details of the major clinical studies for the CNS indication will be discussed in section 5.2.

**Table 3: Overview of All Clinical Studies for Dotarem Efficacy and Safety in Various Indications**

<b>Study # Study year Study sites location(s )</b>	<b>Subject Age Range (yrs) Total # Subjects # Subjects exposed (Study Drug)</b>	<b>Study Phase</b>	<b>Study drug Dosage (route: Intravenous)</b>	<b>Study Indication or Type of Study; Major Efficacy Summary</b>	<b>Study Objectives; Synopsis</b>
DGD-3-6; 1987; UK	21-29; 6; 6	1	0.1 mmol/kg	PK(healthy volunteers); 2 compartment model suggested; blood and urine samples up to 48 hours	Study of the excretion of Dotarem in the blood, urine, and feces of healthy male volunteers
DGD-3-28; 1990; France	20-59; 12; 12	1	0.1 mmol/kg	PK ( 4 healthy volunteers; 8 renal failure subjects); PK parameters and lab	Study of the pharmacokinetics of Dotarem in patients with

				safety, decreased clearance with increased renal failure 24 hours excretion 93% for normals, 75% for moderate failure, 49% for severe failure)	chronic renal failure
DGD-3-48; 2004; France	18-45; 32; 32	1	0.1 mmol/kg 0.3 mmol/kg	PK (healthy volunteers); PK parameters following single injection and following triple dose (2 injections); study showed drug drug distribution differences between males and females based on body weight, dose proportionality confirmed, rapid clearance from plasma by renal clearance	Pharmacokinetic study of Dotarem after injection of 0.1 mmol/kg dose and 0.1 + 0.2 mmol/kg dose in healthy male and female volunteers
DGD-44-39; 2004; France	19-75; 40; 40	2	0.3 mmol/kg	QT study; crossover; subjects received both Dotarem and 0.2 mmol/kg as 2 doses and placebo; no effect on QT or QTc interval or other ECG parameters	12-lead ECGs, 2 day washout between treatments; major criteria were QT and ATc intervals according to Bazett and Fredericia's formula; secondary criteria of multiple ECG criteria, AUC determinations, vital signs, lab parameters
DGD-3-17; 1988; France	18-77; 20; 10	2	0.1 mmol/kg	CNS imaging for diagnostic confidence, various neurological	Randomized double blind comparative

				conditions; 82% modified diagnosis compared to 40% for Magnevist with therapeutic management changed for 4/9 with Dotarem and 4/4 with Magnevist;	parallel group study comparing efficacy and safety of Dotarem to Magnevist
DGD-3-31; 1988; France, Belgium, Switzerland	18-79; 299; 149	3/4	0.1 mmol/kg	CNS imaging for diagnostic usefulness/confidence and assistance in management, various neurological conditions similar for both drugs	Randomized double blind comparative parallel group study comparing efficacy and safety of Dotarem to Magnevist
DGD-3-07; 1987 France	18-82; 56; 56	2	0.1 mmol/kg	CNS (53) and bone and soft tissue (3) for comparison and diagnostic contribution of contrasted images as versus CT and non contrast images; modification of diagnosis in 51%, change in management in 45%;	Neurological (53) and bone and soft tissues (#) magnetic resonance imaging, general safety and diagnostic efficacy
DGD-3-11; 1987; France	24-76; 19; 19	2	0.1 mmol/kg	CNS study for cerebral safety, clotting, and diagnostic efficacy; most with good or excellent diagnostic contribution with modification or specification of diagnosis in 68% and change in management in 47%;	MRI for neurological investigation for cerebral safety, effects on clotting, and diagnostic efficacy in neurological investigations
DGD-3-04; 1987; France	17-72; 20; 20	2	0.1 mmol/kg	CNS, neurological investigations for etiological diagnosis,	Renal and hepatic safety and diagnostic

				assessment of lesions, investigation of recurrence or postoperative review; efficacy compared to uncontrasted studies was primarily an excellent contribution with 75% modification in diagnosis and 85% modification of therapeutic approach; safety for 42 serum and urine parameters before injection and at 24 hours (minor variations in hematologic parameters remaining within normal range except for sodium and CO2 which were elevated pre study also and for 2 urinary parameters of creatinine clearance and BUN, for AEs (none), and visual analogue scale (minor discomfort)	efficacy in neurological investigations
DGD-3-08; 1987; France	20-72; 54; 54	3	0.1 mmol/kg	CNS comparing Dotarem to preliminary exams; contrasted imaging superior to CT and to non contrasted imaging with change in therapeutic management in 96%;	MRI for general safety and diagnostic efficacy
DGD-3-01; 1987; France	21-66; 10; 10	2	0.1 mmol/kg	CNS study for detection and characterization of lesions, contribution of MRI contrast study,	MRI for renal safety and diagnostic efficacy in neurological

				and safety; diagnostic contribution of contrasted mostly good with change in diagnosis in 70% and change in management in 60%	investigations
DGD-3-12; 1987; France	18-76; 50; 50	2	0.1 mmol/kg	CNS for the value of Dotarem in lesion detection and assessment; efficacy post contrast mostly good or excellent with change in diagnosis in 67% and modification of therapeutic management in 61%	MRI for general safety and diagnostic efficacy in neurological investigations
DGD-3-14; 1987; France	18-70; 55; 55	3	0.1 mmol/kg	CNS for assessment of the diagnostic contribution of contrast to non contrasted studies; modification of diagnosis in 69% and revision of therapeutic management in 73%;	General safety and diagnostic efficacy of Doterem in cerebrospinal MRI
DGD-3-23; 1988 France	18-69; 50; 50	3	0.1 mmol/kg	CNS to evaluate the diagnostic contribution of contrast to efficacy by visualization parameters and by contribution to diagnosis; contrast showed improved efficacy when compared to CT and when compared to non contrasted images and resulted in change in diagnosis in 15% of cases with change in	Neurological magnetic resonance imaging, general safety and diagnostic efficacy

				therapeutic approach in 29%	
DGD-3-5; 1987; Belgium	18-74; 10; 10	2	0.1 mmol/kg	CNS efficacy determined good or excellent diagnostic contribution for the contrasted exams (better tumor characterization); modification of diagnosis in 50% and modification of therapeutic management in 30%	Neurological investigation by magnetic resonance imaging, laboratory safety and diagnostic efficacy
DGD-3-9; 1988; Belgium	25-75; 22; 22	2	0.1 mmol/kg	CNS to study safety and efficacy in neurological investigations; efficacy for good or excellent diagnostic contribution with contrasted images and change in diagnosis in 45% and change in therapeutic management in 36%	Dotarem renal and hepatic safety and general safety and diagnostic efficacy in neurological investigations
DGD-3-3; 1988; France	21-75; 30; 30	2	0.1 mmol/kg	CNS safety assessed by 15 hematological parameters before injection and at 2, 9, and 24 hours post injection	Hematological safety and diagnostic efficacy in patients undergoing neurological investigation by magnetic resonance imaging
DGD-3-21; 1988; France	16-80; 50; 50	3	0.1 mmol/kg	CNS to evaluate the diagnostic contribution of contrast to efficacy by visualization parameters and by contribution to	Neurological magnetic resonance imaging, general safety and diagnostic efficacy

				diagnosis; contrast showed improved efficacy when compared to CT and when compared to non contrasted images and resulted in change in diagnosis in 78% of cases with change in therapeutic approach in 74%	
DGD-3-20; 1988; France	24-72; 48; 48	3	0.1 mmol/kg	CNS imaging as part of ophthalmological and ENT investigations (particularly in retrocochlear pathologies); contrast improved ophthalmologic and ENT pathologies	Magnetic resonance imaging general safety and diagnostic efficacy
DGD-3-33; 1994; France, Belgium	21-81; 65; 65	3	0.3 mmol/kg	CNS study of brain metastases for evaluation of efficacy and safety using triple dose versus a standard dose; triple dose useful for detection in 89% of cases compared to standard dose	Evaluation of the diagnostic efficacy and clinical safety of triple dose dotarem in comparison to the standard dose for the detection of brain metastases;
DGD-3-34; 1994; France, Switzerland	20-82; 45; 45	2/3	0.3 mmol/kg	CNS; lesion detection and character; additional dose provided more information	Evaluaiton of safety and diagnostic efficacy of triple dose Dotarem in the detection of brain tumors; patients with confirmed or suspected tumors; 0.1 mmol/kg dose

					followed by 0.2 mmol/kg in 30 minutes
DGD-3-40; 1999; France, Belgium, Switzerland, Luxembourg	54-88; 59; 59	4	0.2 mmol/kg	CNS for clinical evaluation of Alzheimer Disease; controversial value for early detection of perfusion disorders	Evaluation of cerebral functional MR imaging with Dotarem in the diagnosis of Alzheimer disease; 4 study groups based on dementia status including normal subjects; MR perfusion sequences with relative perfusion scoring measurements in several areas of the cerebral cortex testing correlation with perfusion scores and clinical stages, hypothesizing reduced perfusion in the temporo-parietal cortex
DGD-3-44; 2003; France, Germany	18-79; 151; 150	3	0.1 mmol/kg	CNS efficacy for sensitivity and specificity did not show significant difference between image sets	CNS study to confirm the efficacy of Dotarem enhanced MRI to a non enhanced MRI in the characterization of cerebral and spinal tumors using histology as "standard of truth"
DGD-3-15;	0.04-17;	2	0.1 mmol/kg	CNS to study safety	CNS study for

1988; France	29; 29			and efficacy in neurological investigations; efficacy for better or complementary diagnostic contribution with contrasted images in 69% and change in therapeutic management in 34%	efficacy and safety in children ages 0-18 years
DGD-3-16; 1988; France	0.5-17; 20; 20	2	0.1 mmol/kg	CNS to study safety and efficacy in neurological investigations; efficacy for better or complementary diagnostic contribution with contrasted images in 94% and change in therapeutic management in 15%	CNS study for efficacy and safety in children ages 0-18 years
DGD-3-29; 1991; France	1-17; 50; 50	4	0.1 mmol/kg	CNS to study safety and efficacy in neurological investigations; efficacy for better or complementary diagnostic contribution with contrasted images in 80% and variable change in therapeutic management in 10% or more	CNS study for efficacy and safety in children ages 0-18 years
DGD-44-50; 2010; USA, Latin America, Europe, South Korea	3-95; 402; 278	3	0.1 mmol/kg	CNS efficacy for lesion characterization and comparison to Magnevist as secondary, Dotarem enhanced images superior and similar to	Safety and efficacy evaluation of Dotarem in magnetic resonance imaging (MRI) in patients with

				Magnevist	central nervous system (CNS) lesions
DGD-3-02; 1987; France	21-76; 20; 20	2	0.1 mmol/kg	Whole Body lesion assessment/follow up; all subjects with good or excellent visualization	Trial conducted for evaluation of bones and soft tissues
DGD-3-13; 1987; France	35-73; 30; 30	3	0.1 mmol/kg	Whole Body imaging (liver) using either 0.2 or 0.4 mL/kg with similar efficacy	Three groups of 10 subjects to evaluate images before and after injection
DGD-3-19; 1987; France	20-84; 39; 39	3	0.1 mmol/kg (18) 0.2 mmol/kg (21)	Whole Body imaging (liver); image quality unchanged with dose	Contribution of imaging before and after injection
DGD-3-22; 1988; France	21-79; 24; 24	3	0.1 mmol/kg	Whole Body imaging (liver); better definitions of hepatic lesions after contrast	Subjects with suspected liver disease also undergoing CT and ultrasound exams
DGD-3-26; 1989; France	28-85; 20; 10	4	0.1 mmol/kg	Whole Body imaging in patients with chronic renal failure; diagnostic quality improved after contrast	Diagnostic efficacy of MRI investigation of the kidney without and with Dotarem; 2 parallel groups (injected with either Magnevist or Dotarem)
DGD-3-32; 1994; France, Belgium	37-77; 80; 80	3	0.1 mmol/kg	Whole Body breast imaging; may be of value when other studies are equivocal	Diagnostic efficacy of Dotarem for the early diagnosis of breast cancer; patients with known tumors (equivocal diagnosis) requiring histological confirmation of

					malignancy
DGD-3-49; 2003; France, Belgium	18-87; 120; 120	3	0.1 mmol/kg	Whole Body to characterize focal hepatic lesions with and without Dotarem; no statistically significant difference for efficacy but therapeutic management helped with contrast	Evaluation of MRI with Dotarem in the characterization of focal hepatic lesions
DGD-3-50; 2003; France	26-87; 110; 109	3	0.1 mmol/kg	Whole Body study to assess efficacy of imaging with and without contrast using a corroborative diagnosis of biopsy, surgery, or cytology; efficacy results were non-conclusive	MRI with Dotarem to characterize abdominal and pelvic lesions
DGD-44-44; 2008 France, Belgium, Italy, Spain	22-92; 114; 70	4	0.1 mmol/kg	Whole Body (Renal Safety), safety study only in subjects with stable stage III or stage IV renal insufficiency, comparing 72 hour creatinine value and eGFR values to baseline in subjects who received Dotarem and subjects who did not receive Dotarem, 25 % value as significant, 1/70 subjects	Renal safety evaluation after Dotarem enhanced MRI compared with non enhanced MRI in patients at high risk for developing contrast medium induced nephropathy
DGD-3-36; 1998; France	24-84; 41; 41 1 withdrawn from efficacy analysis	3	0.1 mmol/kg	MRA for renal artery stenosis; satisfactory sensitivity and specificity	Primary objective was to assess efficacy of Dotarem for renal artery stenosis when compared to DSA

DGD-3-37; 1998; France, Austria	27-89; 35; 35	3	0.05 or 0.1 mmol/kg	MRA for pulmonary embolism; no dose differences; Dotarem results improved over scintigraphy, exam time decreased from DSA	Sensitivity and specificity for diagnosis of pulmonary embolism at 0.05 and 0.1 mmol/kg (twice for each dose)
DGD-3-38; 1998; Switzerland, Belgium	55-81; 40; 40	3	0.1 mmol/kg	MRA for carotid artery stenosis; sensitivity and specificity similar between uncontrasted and contrast studies but more assessable segments with contrast	Comparison of MRA to DSA for carotid artery stenosis
DGD-3-39; 1998; France, Austria	35-84; 40; 40	3	0.05 or 0.1 mmol/kg	MRA for lower limb arterial stenosis; no significant difference between doses, high specificity and low sensitivity	Sensitivity and specificity of Dotarem for stenosis compared to DSA using two doses, each administered twice
DGD-3-42; 2004; The Netherlands	31-72; 6; 6	4	0.125 or 0.250 mmol/kg	MRA for non coronary arterial disease comparing subject level diagnostic agreement with each MRA method with x-ray angiography; efficacy showed higher accuracy with Dotarem MRA	Evaluation of Dotarem enhanced MRA compared to time of flight MRA in the diagnosis of clinically significant non-coronary arterial disease
DGD-44-38; 2006; USA	25-87; 100; 100	3	0.1 mmol/kg	MRA for non coronary arterial disease comparing subject level diagnostic agreement with each MRA method with x-ray angiography; efficacy showed higher accuracy with	Evaluation of Dotarem enhanced MRA compared to time of flight MRA in the diagnosis of clinically significant non-coronary arterial

				Dotarem MRA	disease
DGD-44-42; 2008; South Korea	21-86; 92; 92	4	0.1 mmol/kg	MRA for non coronary arterial disease comparing subject level diagnostic agreement with each MRA method with x-ray angiography; efficacy showed higher accuracy with Dotarem MRA	Evaluation of Dotarem enhanced MRA compared to time of flight MRA in the diagnosis of clinically significant non-coronary arterial disease
DGD-44-46; 2009; USA	23-85; 33; 33	3	0.1 mmol/kg	MRA for evaluation of Dotarem enhanced MRA compared to TOF MRA in the diagnosis of renal arterial disease; premature termination of study, no efficacy analysis	Comparison of MRA TOF images and Dotarem images with CTA (renal arterial disease)
DGD-44-47; 2009; USA, Canada	26-80; 13; 13	3	0.1 mmol/kg	MRA for evaluation of Dotarem enhanced MRA compared to TOF MRA in the diagnosis of renal arterial disease; premature termination of study, no efficacy analysis	Comparison of MRA TOF images and Dotarem images with CTA (renal arterial disease)
DGD-44-48; 2009; USA, Columbia, Argentina, Mexico, South Korea, Chile	20-97; 222; 222	3/4	0.1 mmol/kg	MRA for carotid and vertebral basilar artery stenosis comparing TOF and contrasted images to CTA; efficacy showed decreased technical failure rate with Dotarem and non inferior specificity but no significant difference in sensitivity	Comparison of MRA TOF images and Dotarem images with CTA (cervical artery disease)
DGD-44-49; 2009;	21-87; 211; 211	3/4	0.1 mmol/kg	MRA for carotid and vertebral basilar	Comparison of MRA TOF images

USA, South Africa, Argentina, Mexico, South Korea, Chile				artery stenosis comparing TOF and contrasted images to CTA; efficacy showed decreased technical failure rate with Dotarem and non inferior specificity but no significant difference in sensitivity	and Dotarem images with CTA (cervical artery disease)
DGD-44-45; 2010; Austria, Germany, France, Italy, Spain	24-91; 189; 92	3/4	0.1 mmol/kg	MRA successful for efficacy comparing percent agreement between Dotarem and Gadovist to DSA with non inferiority of Dotarem to Gadovist	Comparison of Dotarem enhanced MRA to Gadovist enhanced MRA in the diagnosis of clinically significant abdominal or lower limb arterial disease
DGD-44-52; 2009; Germany	45-77; 20; 20	4	0.1 mmol/kg	MRA for efficacy comparing diagnostic performance (essentially similar)	Comparison of Dotarem enhanced MRA to Gadovist enhanced MRA in the diagnosis of clinically significant abdominal or lower limb arterial disease
<b>Total Subjects N = 2813</b>					

*Reviewer's Comments:*

1. No PK studies were conducted in the pediatric age group.
2. No dose ranging studies were conducted for the CNS indication.

3. *There were no preclinical studies conducted in juvenile animals, (see study summaries).*

3. *3 dedicated studies conducted in children (N = 99) included 7 subjects age 17 years (N = 92) with only 7 subjects ages 0-23 months and only 2 subjects with laboratory safety assessments/vital signs.*

4. *Based on lack of pre-clinical data, PK data, dose ranging studies, and limited pediatric safety assessment, this reviewer does not recommend product approval for the 0-23 month age group.*

5. *Data for the 2-17 year age group is also limited although safety parameters were assessed for the DGD-44-50 clinical trial. Recommendation for approval in this age group will be discussed pending review by pharm/tox and clinical pharmacology.*

## 5.2 Review Strategy

For purposes of review, study DGD-44-050 is interchangeable with -050 and study DGD-44-051 (a re-read of study DGD-3-44) is interchangeable with -3-44 and -051. For evaluation of efficacy, this reviewer concentrated on the two pivotal phase 3 trials with supportive efficacy for the pediatric indication from the 3 phase 2 studies in children.

- **Phase 3 Study DGD-44-050:** "Safety and efficacy evaluation of Dotarem® in magnetic resonance imaging (MRI) in patients with central nervous system (CNS) lesions (SENTIO Study)"
- **Phase 3 Study DGD-44-051:** "Evaluation of MRI with Dotarem® in the diagnosis or follow up assessment of cerebral or spinal tumors. Re-reading of MRI images"
- **Phase 2 Study DGD-3-15:** "G449.06-Magnetic resonance imaging simple, open, phase II in pediatrics"
- **Phase 2 Study DGD-3-16:** "G449.06-Magnetic resonance imaging phase II open-label trial in paediatrics"
- **Phase 4 Study DGD-3-29:** "Evaluation of the efficacy and safety of Dotarem (Gadolinium-DOTA) in MRI of the central nervous system in children"

The focus of the efficacy review was evaluation of the primary efficacy endpoint of the phase 3 trials to demonstrate superiority of the combined unenhanced and Dotarem enhanced MRI over unenhanced MRI using lesion characteristics (assessment of

border delineation, degree of contrast enhancement, and internal morphology of the lesions) in CNS lesions with a disruption of the blood brain barrier (BBB) and/or with abnormal vascularity (including tumoral, vascular, inflammatory, or infectious diseases).

In addition, certain secondary variables of the phase 3 studies were also considered in detail by this reviewer. These included the comparison of Dotarem®-enhanced MRI with Magnevist®-enhanced MRI as well as the evaluation of safety and efficacy of Dotarem® in a pediatric population

Efficacy in the pediatric population was assessed for 38 subjects ages 2-17 years enrolled in the -050 study with analysis for lesion visualization, number of lesions, image quality, confidence in diagnosis, signal intensity and inter and intra reader agreement. The three dedicated CNS pediatric studies were conducted in 99 subjects under age 18 with analysis for image quality and diagnostic contribution.

For evaluation of safety, this reviewer included all the information from the 49 clinical trials (50 subjects treated with Dotarem in phase 1 trials, 390 subjects treated with Dotarem in phase 2 trials, 2079 subjects treated with Dotarem in phase 3 trials, and 294 subjects treated with Dotarem in phase 4 trials). 371 subjects in clinical trials received Magnevist and other gadolinium agents. The total number of clinical trial studies conducted by Guerbet using Dotarem including additional whole body studies (9) and MRA studies (13) was 49 and includes 6 phase 4 studies, 27 phase 3 studies, 12 phase 2 studies, and 4 PK studies with 1 of the PK studies considered to be a phase 2 study. By body region, there were 3 PK studies, 1 cardiac study, 23 CNS studies, and 22 studies of other body regions. Safety evaluation included evaluation of 5 post marketing studies (a 6<sup>th</sup> study is ongoing) and global pharmacovigilance reports.

*Reviewer's Comment: The Applicant noted 6 postmarketing studies however since one of these studies (SECURE Study) is ongoing, this was not considered in the safety review.*

## **5.2 Discussion of Individual Studies/Clinical Trials**

Referral for the SPA pivotal phase 3 trial (DGD-44-050 or-050) was from subjects scheduled to undergo a routine contrast enhanced MRI of the CNS with at least 1 highly suspected or known CNS lesion, both intracranial and spinal, with disruption of the blood/brain barrier and/or with abnormal vascularity (including tumoral, vascular, inflammatory or infectious diseases) based on the results of previous imaging procedures. Referral for the second phase 3 pivotal trial, DGD-44-051 (or -051, original trial DGD-3-44) was for known tumoral disease only. The 3 pediatric trials were conducted for safety and diagnostic efficacy of Dotarem in pediatric CNS imaging.

According to the tables (Tables 4 and 5 below) provided by the applicant, the main referral diagnoses for study -050 were for primary or metastatic brain disease by percentage were as follows: primary brain disease (67.4%), metastatic disease (19.7%). About 3% each were for vascular processes, inflammation, and infection with 3% noted either as other, unspecified tumor, or unknown. For study -051, 62.9% of referrals were for primary brain tumors, 1.2% was for metastatic disease, and 15.9% were unspecified as there was no histology available for these tumors.

As noted in Table 6, no subjects in study -051 were referred for evaluation of the spinal cord. 17 (4.2%) of subjects in the -050 were referred for spinal cord disease.

The 3 clinical trials that were conducted in children were primarily efficacy evaluations in children scheduled for neurological evaluations. Most subjects were referred for a known diagnosis and were scheduled for evaluation or follow up.

**Table 4: Referral Diagnoses Study DGD-44-050**

<b>Referral Diagnosis</b>	<b>Total Patients N (402)</b>	<b>%</b>
Primary brain disease	271	67.4
Metastatic disease	79	19.7
Unspecified tumor disease	2	0.5
Inflammation	13	3.2
Vascular processes	15	3.7
Infection	11	2.7
Other	6	1.5
Unknown	5	1.2

**Table 5: Referral Diagnoses Study DGD-44-051**

Referral Diagnosis	Total Patients N (151)	%
Primary brain tumor	95	62.9
Metastatic disease	32	21.2
Unspecified (no histology)	24	15.9

**Table 6: Spinal Cord Evaluation in Pivotal Studies**

Study Number	Total Number of Subjects	Number and Percent of Subjects Referred for Spinal Cord Evaluation
DGD-44-050	402	17 (4.2%)
DGD-44-051	151	0 (0%)

*Reviewer's Comments:*

- 1. Referral diagnoses for the -050 study were largely tumoral (87.6%) with only 13.2% referred for inflammation which included multiple sclerosis. Based on the small percentage of referrals for non tumoral processes, this reviewer's opinion is that this study may not be representative of the proposed population.*
- 2. Referral diagnoses for the -051 study were limited to a population with known tumor only. For study -051 and the original study DGD3-44, results were largely based on analysis of single lesions based on the Applicant's listings of the number of lesions per subject noted by the readers. Based on tissue diagnosis of these lesions, approximately 75% were malignant. Based on limitations of the population studied, this reviewer's opinion is that this study is not representative of the proposed population.*
- 3. Overall, approximately 3.2% of referrals (17/553) were for spinal cord evaluation. This reviewer's opinion is that this is also a limitation of the study and the study may not represent the proposed population.*

The pivotal phase 3 clinical trial DGD-44-050 and the re-read of study GD3-44 were designed and performed to demonstrate superiority of the combined unenhanced and Dotarem enhanced MRI over unenhanced MRI using lesion characteristics. The

efficacy endpoints were based on three variables: degree of contrast enhancement, border delineation, and internal morphology. The re-read study was designed with an identical analysis to the -050 study. Both studies had similar design elements of subject referral for CNS lesions although referral for the -051 study was limited to tumoral disease only, use of unenhanced and contrast-enhanced images, and MRI sequences. Images for the -050 study were acquired using a 1.5 or 3.0 Tesla magnet whereas a 1.5 Tesla magnet was used at 8/9 of the -051 study sites (1 T magnet at one site). The studies differed in design. Study -050 was a multicenter, randomized, double-blind, fixed sequence, active comparator study (Magnevist as comparator). Study -051 was a multicenter open label study, fixed sequence, comparative study (subject as his/own control). Both had similar endpoints with the -050 study having an additional secondary endpoint of comparison to the comparator drug and the -051 having an additional endpoint of image impact on therapeutic management. A prospectively written blinded image evaluation by 3 independent readers was planned in order to facilitate an independent evaluation and a blinded read manual was submitted. Quality control and quality assurance of the MR images and conduct of the blinded readings was done at the image core laboratory, (b) (4)

More detailed background on the pivotal studies and supportive studies for the 0-23 months age group for the CNS indication is provided in Tables 7 and 8 below.

**Table 7: Phase 3 Pivotal Studies**  
**Study Number DGD-44-050**  
**Study Number DGD-3-44/44-051**

<b>Parameter</b>	<b>Study DGD-44-050</b>	<b>Study DGD-3-44/44-051</b>
Protocol date/amendments	Original: 7-29-10 (SPA)	Original: 7-24-00 Amendment 1: 4-26-02 (revisions relating to inclusion, diagnosis, definition of terms, safety among other) Amendment 2: 3-31-03 (added standard of truth and increased safety monitor to 72 hours)
Study dates	9/10-11/11	8/03-10/04 (3-44) 9/10-2/11 (-051)
Design and schedule	Phase 3, multicenter, randomized, double-blind, comparative study; 3 blinded readers	Phase 3, multicenter, open-label study; 3 blinded readers Two image sets for each

	<p>Two MRIs for each patient:</p> <ul style="list-style-type: none"> <li>• Unenhanced MR Image Set T1W, T2W, FLAIR, with images sent to the core lab (sagittal images mandatory for spine lesions)</li> <li>• Dotarem® Enhanced MR Image Set consisting of a single steady-state sequence, (T1W) or</li> <li>• Magnevist Enhanced MR Image Set consisting of a single steady-state sequence, (T1W)</li> </ul> <p>1.5 or 3 T magnet field</p>	<p>patient: unenhanced MRI and enhanced MRI with Dotarem (unenhanced MRI consisting of steady-state sequences [T1-weighted, T2-weighted], and Dotarem-enhanced MRI consisting of steady-state sequences T1-weighted)</p> <p>1 or 1.5 T magnet field</p>
Inclusion criteria	Referral for contrast-enhanced MRI of the CNS based on results from a previous imaging procedure; glomerular filtration rate (GFR) value $\geq 30$ mL/min/1.73m <sup>2</sup> derived from a serum creatinine result within 7 days prior to study enrollment	Referral for contrast-enhanced MRI of the CNS based on suspicion of or known CNS tumoral lesion; likely to undergo biopsy or surgery
Exclusion criteria	Unstable clinical presentation; acute or chronic renal insufficiency; CHF or long QT syndrome; contraindication to MRI such as pacemaker; known allergy to gadolinium chelates	Diffuse non tumoral disease such as Alzheimers Disease; contraindication to MRI such as pacemaker; known allergy to gadolinium chelates; recent gadolinium or iron nanoparticle exam
Test product dose	Dotarem 0.1 mmol/kg administered by IV bolus about 2 mL/sec for adults and 1 mL/sec for pediatric population;	Dotarem 0.1 mmol/kg 1-2 mL/sec administered IV manually or by power injector
Reference therapy (Comparator)	Magnevist administered to adult population only (2:1 ratio Dotarem:Magnevist), also 0.1 mmol/kg at 2 mL/sec	None
Primary objectives	To demonstrate superiority of the combined unenhanced and	To demonstrate superiority of the combined unenhanced

	Dotarem enhanced (paired) MRI over unenhanced MRI using lesion characteristics as per efficacy variables	and Dotarem enhanced (paired) MRI over unenhanced MRI using lesion characteristics as per efficacy variables
Secondary objectives; therapeutic management	To compare Dotarem enhanced MRI with Magnevist enhanced MRI in terms of lesion evaluation; to evaluate enhanced MRI compared to unenhanced MRI by lesion counting, signal intensity, image quality, and diagnostic confidence; to compare Dotarem enhanced MRI to Magnevist enhanced MRI for variables just noted; to evaluate lesion visualization by on site readers; to assess inter and intra reader agreement for off site readings; to assess clinical and biological safety of Dotarem compared to Magnevist; to evaluate safety and efficacy of Dotarem in a pediatric population	To assess efficacy in terms of lesion visualization; to count and compare lesion numbers identified by each modality; to rate/measure and compare image quality, diagnostic confidence, signal intensity, and signal to noise ratio; to assess inter and intra reader agreement; to assess changes of therapeutic management before and after injection
Efficacy variables	Border delineation (3 point scale) Degree of contrast enhancement (3 point scale) Internal morphology of lesions (3 point scale)	Border delineation (3 point scale) Degree of contrast enhancement (3 point scale) Internal morphology of lesions (3 point scale)
Safety evaluation and monitoring	History and physical and signing the informed consent, laboratory and hematological parameters and urinalysis as baseline screening and at 24 hours post injection; eGFR within 7 days prior to study; pregnancy test within 24 hours prior to study; 100 subjects to have 12 lead ECG within 24 hours prior to injection and 30 minutes post injection; vital signs immediately prior to injection and at 5 minutes, 15 minutes, and 24 hours after injection; injection site	Adverse events and vital signs up to 24 hours post injection

	tolerance at 24 hours post injection; adverse events from the time of signing informed consent to the last safety visit performed	
Outcome measures/data analysis	Blinded image evaluation performed in a core laboratory by independent experienced radiologists (3) trained in the study design, to consist of 3 reading sessions: pre (uncontrasted images, post (contrasted images), and paired (pre + post images)  One on site radiologist responsible for similar reads	Blinded image evaluation performed in a core laboratory by independent experienced radiologists (3) trained in the study design, to consist of 3 reading sessions: pre (uncontrasted images, post (contrasted images), and paired (pre + post images)  One on site radiologist responsible for similar reads
Blinded read	Prospectively defined blinded reading image evaluations and centralized defined in the original protocol; included image quality assurance, reader selection and training, and reader training; minimum of two week separation between reading sessions to minimize recall bias; blinded read charter, 5-24-10	Prospectively defined blinded reading image evaluations defined in the re-read protocol; blinded read charter 5-24-10
Statistical analysis plan	7/29/10; included in the SPA agreement	7/29/10; same SAP as per the -050 study
Primary statistical hypotheses	3 efficacy variables tested for superiority of gadobutrol-enhanced MRI versus unenhanced MRI using regression models, null and alternative hypotheses as follows: $H_0$ : combined unenhanced and Dotarem mean = unenhanced MRI mean versus $H_1$ : combined unenhanced and Dotarem mean $\neq$ unenhanced MRI mean The study was to be considered	3 efficacy variables tested for superiority of gadobutrol-enhanced MRI versus unenhanced MRI using regression models, null and alternative hypotheses as follows: $H_0$ : combined unenhanced and Dotarem mean score = unenhanced MRI mean score (one sided $\alpha = 0.025$ as statistically significant) versus

	successful if 2 out of the 3 readers simultaneously met the alternative hypothesis ( $\mu_1 > \mu_0$ ; $1-\beta = 0.80$ in the Dotarem group with a statistically significant ( $p \leq 0.025$ ) positive mean score per patient for all 3 co-primary endpoints	$H_1$ : combined unenhanced and Dotarem mean $\neq$ unenhanced MRI mean (average minimum patient score if there is benefit with Dotarem > average score in case of no benefit; $1-\beta = 0.80$ ); 2/3 readers to meet alternative hypothesis simultaneously
Handling of missing data	No imputations for missing data from early termination, missed evaluations, or other; if no scores for lesions on pre and paired, not included in analysis; if on pre or paired only, then included in analysis; if non assessable on one of the two MRI modalities, then the missing endpoint of the other modality will default to 0 and subject will be included in analysis	No imputations for missing data from early termination, missed evaluations, or other; if no scores for lesions on pre and paired, not included in analysis; if on pre or paired only, then included in analysis; if non assessable on one of the two MRI modalities, then the missing endpoint of the other modality will default to 0 and subject will be included in analysis
Analysis sets	Safety analysis-395 subjects,(357 adults total, 240 adults and 38 pediatric subjects received Dotarem; 117 adults received Magnevist) FAS/ITT* (all exams, may have protocol violations): 393, (356 adults/37 ped. 276 Dotarem/117 Magnevist) PPS** : 382 (348 adults/34 ped, 266 Dotarem/116 Magnevist) AIP***-416 enrolled (377 adults, 39 peds) 364 randomized (245 Dotarem/119 Magnevist/38 peds) EE****-variable by reader	Safety analysis-150 subjects Efficacy analysis (FAS/ITT)*-149 subjects Efficacy analysis (PPS)**-124 subjects All included set (AIP)***-151 EE****-129 (variable by reader)

\* FAS (ITT) = Full Analysis Set; all subjects with endpoint assessments

\*\* PPS = Per Protocol Set; all subjects with no protocol violations

\*\*\* AIP = All Included Set; all subjects analyzed for demographic data, medical history, concomitant medication, and withdrawals

\*\*\*\* EE = Efficacy Evaluable; variable number by reader

*Reviewer's Comment: Administration rate of Dotarem to adults varied between the two studies, (2 mL/sec for -050 and 1-2 mL/sec for -051). Additionally, the rate reported for the -050 study (1 mL/sec) differs from that reported for the pediatric studies in Table 8 below and differs from recommendations of 1-2 mL/sec in the proposed package insert.*

**Table 8: Pediatric CNS Support Studies-DGD-3-15, DGD-3-16, DGD-3-29**

<b>Parameter</b>	<b>DGD-3-15</b>	<b>DGD-3-16</b>	<b>DGD-3-29</b>
Protocol Title	Magnetic Resonance Imaging. Simple. Open. Phase II. In Pediatrics.	Magnetic resonance imaging, Phase II open-label trial in pediatrics.	Evaluation of the efficacy and safety of Dotarem (gadolinium DOTA) in MRI of the central nervous system in children. Open-label phase IV clinical trial. 50 patients.
Study dates	2/88-6/88	6/1/88-6/29/88	1/90-3/91
Design and schedule	Single-center, open label study to evaluate the renal and hepatic laboratory safety, overall safety, and diagnostic performance of G.449-06 in 29 children	Single-center, open label study to evaluate the general safety and diagnostic performance of G.449-06 in 20 children	Single-center, open label study to evaluate the general safety and efficacy of Dotarem in 50 children
Inclusion and exclusion criteria	Children ages newborn through 17 years scheduled for neurological investigation by magnetic resonance imaging; exclusion for a known history of renal or liver failure or surgery within the past 3 or 6 months depending upon disease	Children ages newborn through 17 years scheduled for neurological investigation by magnetic resonance imaging; exclusion for a known history of renal or liver failure or surgery within the past 3 months	Children under 18 years of age; exclusion for contraindication to MRI study such as ferromagnetic clips
Age range and	0.1-<18.0 years; 7.9	0.5-<18 years; 10.1	1-<18 years; 8.8

mean age of enrolled patients	years	years	years
Test product dose	0.1 mmol/kg G.449-06 diluted in normal saline or undiluted at a flow rate of 3.0 ml/min	0.1 mmol/kg G.449-06 at a flow rate of 2.4 ml/min	0.1 mmol/kg Dotarem IV, rapid bolus injection possible
Primary objective	To evaluate the renal and hepatic laboratory safety, overall safety, and diagnostic performance of G.449-06 in 29 children scheduled for neurological investigation by magnetic resonance imaging	Diagnostic efficacy	Diagnostic efficacy
Specific objectives	To compare images obtained pre and post contrast for diagnosis and change in therapeutic management; to assess various laboratory parameters in the first 20 subjects studied	To compare images obtained pre and post contrast for diagnosis and change in therapeutic management; safety as a secondary objective	To compare images obtained pre and post contrast for image quality, diagnostic value, and change in therapeutic management; safety as a secondary objective
Safety evaluation and monitoring	Determined by 17 blood parameters pre-injection and 2 and 24 hours post injection for the first 20 patients enrolled; adverse events monitoring for all patients	Adverse events monitoring, time not specified	Adverse reactions for up to 45 minutes post dose
Outcome measures/data analysis	Diagnostic performance evaluated by comparing the results of pre and post	Diagnostic performance evaluated by comparing the results of pre and post	Diagnostic performance for image quality and diagnostic value evaluated by

	contrast injection MRI images in the 29 patients	contrast injection MRI images in the 20 patients	comparing the results of pre and post contrast injection MRI images in the 50 patients
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*Reviewer's Comments:*

1. *Flow rate for study drug administration was different for all three studies, it was permissible to dilute study drug for the phase 2 studies, and bolus injection was used for the phase 4 study. The proposed administration in the NDA label does not reflect these administration methods.*
2. *The total number of pediatric subjects studied based on current FDA groupings (up through age 16) was 130. 2 subjects in the 050 study and 9 other children were age 17.*
3. *As noted in Table 8, study DGD-3-16 assessed adverse events for safety but no assessment times were stated.*
4. *A total of 7 subjects were studied in the 0-23 months age group in these 3 trials with only 2 subjects assessed by laboratory parameters for safety.*

## 6 Review of Efficacy

### Efficacy Summary

Two phase 3 clinical studies performed to support a CNS indication for Dotarem with 3 studies supportive for a pediatric indication:

- Study DGD-44-050 was a comparative randomized phase 3 study with Dotarem and Magnevist, (393 subjects in Full Analysis Set [FAS], 356 adults, 37 pediatric subjects, 276 Dotarem:117 Magnevist)
- Study DGD-44-051 was a re-read of a single arm Dotarem study, (149 subjects in FAS).
- Studies DGD-3-15 and DGD-3-16 were phase 2 single arm Dotarem studies in pediatric subjects ages 0-<18 years (29 and 20 subjects subjects in FAS respectively).
- Study DGD-3-29 was a phase 4 single arm Dotarem Pediatric study, (50 subjects ages 0-<18 years in FAS).

The applicant noted that including the 3 pediatric studies, there were 21 supportive studies for the proposed indication which were selected on the basis of the same body

region as used in the two US IND studies (MRI of the CNS). The applicant noted that all supportive studies demonstrated the efficacy of Dotarem-enhanced images for diagnostic confidence, image quality, and therapeutic management as compared to unenhanced images.

Further details regarding the efficacy results of these studies are included in the sources of clinical data, section 5.1, tables of clinical studies, Tables 3-5.

The two US phase 3 IND studies (DGD-44-050 and DGD-44-051 which is a re-read of DGD-3-4) are the focus of the evaluations designed to demonstrate efficacy of Dotarem at a dose of 0.1 mmol/kg body weight (BW) for the CNS indication. The 3 pediatric studies were designed to demonstrate efficacy for CNS lesions in this population.

The 2 pivotal phase 3 studies were similar for some elements of study population and design having the following similarities:

Study population: enrollment of male and female subjects  $\geq 18$  years of age referred for contrast-enhanced MRI of the CNS

Dotarem regimen: all subjects in the phase 3 studies received Dotarem at the targeted dose of 0.1 mmol/kg BW by single i.v. injection

MRI (minimum images obtained): unenhanced MR image set obtained before the Dotarem administration, consisting of at least the steady-state sequences T1w, T2w, and Fluid-Attenuated Inversion Recovery (FLAIR)

Dotarem-enhanced MR image set obtained after the unenhanced image set consisting of at least the steady-state sequences T1w

Blinded reading: the unenhanced MR image set and the combined unenhanced and Dotarem-enhanced MR image set as well as the Dotarem-enhanced images alone were evaluated by three independent blinded readers.

Several different elements of the study population and design were also noted:

Inclusion criteria: suspected disease of the brain or spinal cord (any type) for study -050 versus known tumoral diagnoses for brain lesions for study -051

Ethnicity/race: several countries and ethnicities for study -050 versus 8/9 sites in France and over 97% Caucasian subjects for study -051

Dotarem injection: 2mL/sec injection (adults) for study -050 versus 1-2 mL/sec for study -051

For both of the two above mentioned US IND studies, the primary efficacy evaluations were based on the following three visualization variables:

Degree of contrast enhancement (0=unevaluable, 1=seen, but imperfectly, 2=seen completely/perfectly)

Assessment of border delineation (0=unevaluable, 1=seen, but imperfectly, 2=seen completely/perfectly)

Internal morphology of lesions (0=unevaluable, 1=seen, but imperfectly, 2=seen completely/perfectly)

As secondary variables, the two phase 3 studies evaluated the following with not all variables analyzed for both studies:

- Evaluations by on site readers
- Assessment of inter and intra reader agreement
- Assessment of subjective factors such as image quality, diagnostic confidence, and impact on the therapeutic management of patients, (some factors both studies)
- Evaluation of contrasted (post contrast) images
- Assessment of signal intensity, signal/noise ratio, and lesion number, (some factors both studies)
- Safety assessment in the adult population (parameters varied between studies)
- Comparison of the safety and efficacy of Magnevist to Dotarem in the adult population (for the -050 study only)
- Evaluation of the safety and efficacy of Dotarem in the pediatric population

The pediatric studies were primarily to assess the lesion visualization and patient management in pediatric patients ages 0-<18 years of age.

For both US IND studies, (-050 and the re-read -051), evaluation of the efficacy variables was performed as a prospectively planned evaluation in a centralized manner. This was done by independent radiologists (blinded readers) who were trained for efficacy evaluations to standardize the reading and to minimize variability among the readers. For both of the phase 3 studies, the three primary efficacy visualization variables identified above were assessed for superiority of the combined image set (i.e. unenhanced plus contrast-enhanced images) compared to the unenhanced image set.

The primary efficacy analyses of these three visualization variables were done using the per patient values for each of the three blinded readers with success if 2 out of the 3 readers met the alternative hypothesis for the three co-primary endpoints in the Dotarem group, (i.e.a statistically significant difference in score means in border delineation, morphology, and degree of contrast enhancement). Statistical tests for superiority were one-sided using a complex regression analysis, one sided  $p \geq 0.025$  positive level of significance.

For the 3 pediatric studies, the efficacy analysis was descriptive and comparative with summary statistics for some variables such as demographic data. No formal statistical

analysis of efficacy data was performed. As already noted, pediatric efficacy analysis for the -050 study was a secondary analysis.

For both the -050 and -051 study, the blinded readers' evaluations demonstrated statistically significant superiority of the combined unenhanced/contrast-enhanced MRI to unenhanced MRI for contrast enhancement, border delineation, and internal morphology of lesions. As a secondary efficacy endpoint, superiority of Magnevist for the same 3 variables was demonstrated and scores for the visualization endpoints were higher for the paired images versus the pre (uncontrasted) images for the pediatric population in the -050 study.

Statistical analyses for primary and secondary analyses are discussed in sections 6.1.4-6.1.10.

## 6.1 Indication

For diagnostic magnetic resonance imaging; *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* (b) (4) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

### 6.1.1 Methods

Study DGD-44-050 was a multicenter, randomized, comparative phase 3 study to determine the safety and efficacy of Dotarem in patients referred for contrast-enhanced MRI of the CNS. Enrollment (the recruited all included population or AIP group) of 402 subjects was based on a suspected CNS abnormality. 364 adult subjects were randomized. All subjects received a non contrast MRI exam followed by a contrasted exam with either Dotarem or Magnevist for the adult population (2:1 subject ratio—278 subjects in Dotarem arm, 117 subjects in Magnevist arm). 38 pediatric subjects ages 2-17 years were included in the Dotarem group for secondary endpoint analyses. Study DGD-44-051 was a blinded centralized re-read of the previously conducted DGD-3-44 study. This prior study was a multicenter, open label phase 3 study conducted in Europe to determine the safety and efficacy of Dotarem in 151 subjects presenting with or suspected of having cerebral or spinal tumors who were referred for contrast enhanced MRI of the CNS. Results from 150 subjects were used for the blinded re-read.

For both studies, 3 readers interpreted images in a sequential, locked read manner. The primary endpoints in each study compared paired unenhanced + enhanced images (paired images) to unenhanced images using 3 categories of visualization—border

delineation, internal morphology, and degree of contrast enhancement. For success, superiority of the paired images over the unenhanced images was required for all three endpoint categories for 2 out of 3 readers. The visualization scale for all three variables ranged from 0 to 2 as follows:

Degree of contrast enhancement (0=unevaluable, 1=seen, but imperfectly, 2=seen completely/perfectly)

Assessment of border delineation (0=unevaluable, 1=seen, but imperfectly, 2=seen completely/perfectly)

Internal morphology of lesions (0=unevaluable, 1=seen, but imperfectly, 2=seen completely/perfectly)

In support of the indication to visualize CNS lesions, the applicant noted that an additional 21 studies of the CNS were conducted. The three CNS studies in children enrolled 99 children ages newborn through age 17 years. Note is made that the pediatric age group for the -050 study also included subjects through age 17 years.

*Reviewer's Comments:*

*1. The applicant included several subjects age 17 in the pediatric studies with current FDA pediatric age group studies for ages up to 17 years. This reviewer considers this acceptable in view of additional subject numbers in the -050 study.*

*2. The applicant did not conduct any PK studies in the pediatric population and MRI exams for efficacy were limited to CNS lesions. Although the proposed indication is for CNS efficacy, at least a limited evaluation of whole body distribution might be contributory to safety and proper dose for age and understanding Dotarem distribution in the 0-23 months population.*

### 6.1.2 Demographics

The study population evaluable (both non contrasted and paired MRI modalities) for efficacy includes 353 adult and 37 pediatric subjects from the -050 study and 149 subject for the -051 re-read study for a total of 502 adults for primary analysis and 37 pediatric subjects for secondary analysis in the 2 US IND studies. The patient population that was enrolled in the two studies reflects the proposed indicated patient population, (subjects likely to undergo a contrast-enhanced MRI of the CNS in routine clinical practice). Subjects were eligible for inclusion into the -050 study if they were referred for contrast-enhanced MRI of the CNS, either brain or spine, based on results of prior diagnostic testing. Subjects were not eligible for inclusion if they had either acute or chronic grade IV/V renal insufficiency with  $GFR < 30 \text{ ml/min/1.73 m}^2$ , had

contraindications to MRI exam or known allergy to gadolinium chelates, or if they received contrast agent within 3 days prior to exam or were scheduled to receive contrast agent within 24 hours after the exam. Only subjects with known tumoral disease detected on previous CT or MR imaging and scheduled for biopsy or surgery were eligible for the DGD-3-44 study (the -051 re-read). Exclusions were for non tumoral disease (e.g. diffuse disease such as multiple sclerosis), contra indication to MRI, and known allergy to gadolinium chelates. Tables 10 and 11 below summarize the demographics for the two phase 3 pivotal studies. Table 10 is reproduced from the NDA Clinical Study Report DGD-44-050, section 11.2.1, page 47. Table 11 is reproduced from the NDA Clinical Study Report DGD-3-44, section 11.2.1, page 34.

**Table 9: DGD-44-050 Demographics All Included Population**

Parameter	Treatment		Total N=364
	Dotarem® N=245	Magnevist® N=119	
<b>Age (years)</b>			
Mean	53.17	55.95	54.08
Median	55.10	57.40	55.40
SD	14.35	14.43	14.41
Minimum	18.80	19.00	18.80
Maximum	85.10	94.40	94.40
<b>Sex</b>			
M	114 (46.5%)	54 (45.4%)	168 (46.2%)
F	131 (53.5%)	65 (54.6%)	196 (53.8%)
<b>Ethnic origin</b>			
Caucasian	207 (84.5%)	95 (79.8%)	302 (83.0%)
Asian	27 (11.0%)	15 (12.6%)	42 (11.5%)
Black	9 (3.7%)	8 (6.7%)	17 (4.7%)
Other	2 (0.8%)	1 (0.8%)	3 (0.8%)
<b>Height (cm)</b>			
N	242	119	361
Mean	168.26	167.34	167.96
Median	168.00	168.00	168.00
SD	9.89	9.77	9.85
Minimum	138.00	146.00	138.00
Maximum	194.00	196.00	196.00
<b>Screening Body Weight (kg)</b>			
N	244	118	362
Mean	76.04	76.70	76.26
Median	74.00	75.00	75.00
SD	17.03	16.44	16.82
Minimum	43.00	44.00	43.00
Maximum	136.00	135.40	136.00
<b>Body Mass Index (kg/m<sup>2</sup>)</b>			
N	241	118	359
Mean	26.82	27.30	26.98
Median	26.08	26.84	26.12
SD	5.32	4.89	5.18
Minimum	16.65	16.56	16.56
Maximum	51.30	47.27	51.30

As can be seen in the above table, the demographics for both the Dotarem and the Magnevist populations were similar and may be summarized as follows:

- Approximately 46% of subjects were males with 54% females
- The mean age was approximately 54 years with a range from 19-94 years
- 80% or greater were Caucasian followed by 11-12% Asian

*Reviewer's Comment: The study also included 4.7% Blacks and 0.8% subjects of Other ethnicity however overall the demographics do not reflect the US population.*

**Table10: DGD-3-44 (-051) Demographics All Included Population**

	All (N = 151)
<b>Gender N(%)</b>	
Male	84 (55.6%)
Female	67 (44.4%)
<b>Race N(%)</b>	
Caucasian	147 (97.4%)
Black	1 (0.7%)
Other	3 (2.0%)
<b>Age (years)</b>	
n	151
mean (std)	53.9 (13.5)
median	55.0
min / max	18.0 – 79.0
<b>Weight (kg)</b>	
n	151
mean (std)	73.2 (13.8)
median	72.0
min / max	41.0 – 120.0
<b>Height (cm) *</b>	
n	136
mean (std)	169.8 (9.1)
median	170.0
min / max	141.0 – 197.0
<b>BMI (kg / m<sup>2</sup>) *</b>	
n	136
mean (std)	25.6 (4.0)
median	25.1
min / max	16.9 – 39.2

\* Missing

Using the above table, the demographics may be summated as follows:

- More males (overall 55.6%) than females (44.4%) were included
- All subjects were between the age of 18.0- 79 years which is the anticipated age range for the indication
- Overall, Caucasians accounted for over 97% of the study population; racial distribution in the studies reflected recruitment sites (8 in France, 1 in Germany)

*Reviewer's Comment: The ethnicity of the patient populations enrolled in the DGD-3-44 study is not reflective of the proposed indicated patient population (US demographics).*

### 6.1.3 Subject Disposition

Table 11 below presents subject disposition by analysis set for the two pivotal phase 3 trials. For study DGD-44-050, the disposition reflects comparator drug Magnevist (M) as well as Dotarem (D), both adult and pediatric subjects. All pediatric subjects received Dotarem. From this table it can be sign that a high percentage of subjects completed both studies and most subjects were included in analyses. For the DGD-3-44 study, the number of subjects in the efficacy population differed substantially from the number enrolled based on lack of histological confirmation of tumor however, for the blinded read 149/150 subjects had images that were interpreted for efficacy.

**Table 11: Subject Disposition by Group (2 pivotal studies)**

<b>Parameter</b>	<b>Study DGD-44-050</b>	<b>Study DGD-3-44; -051</b>
Total # patients randomized (AIP*-all included population)	402 364 adults/38 peds 245 D/119 M	151*
Drop outs	7(no study drug) 5D/2 M 2(0.8%), 1 lost to f/u, 1 withdrawal due to technical incident	3 (2.0% of AIP set)*; 1 withdrew consent pre contrast and one post contrast, one due to SAE
Lost to follow up	1 (0.4%)/0 (0.0%)	1*(.03%)
Completed study	238 (97.1%)/117 (98.3%)	129*
Total protocol deviations/Major/Minor	31.9% at least one protocol deviation, 34.7 % Dotarem, 26.1% Magnevist Major-7.7%	25* subjects (major “out of timeframe” or withdrawal)
Safety population	395 357 adults/38 peds 278 D-240 adult /117 M	150*
All Included set	364 245 D /119 M	151*
Efficacy Evaluable (all valid assessments for reading) or Full Analysis Set	393(variable by reader) Per reader-345, 337,354 356 adults/37 peds 276/117(D/M)	129* (variable per reader) 149**
Per protocol set (no significant protocol deviations)	382 (variable by reader) 348 adults/34 peds 266 D/116 M	129* (variable per reader) 124 **

\* Study DGD-3-44  
 \*\* Study DGD-44-051

Table 12 summarizes subject disposition for the two phase 3 pivotal trials based on enrollment, randomization, completion of the trial, and reason for discontinuation.

**Table 12: Subject Disposition by Enrollment/Discontinuation Phase 3 Studies**

<b>Parameter</b>	<b>Study DGD-44-050 # of Subjects</b>	<b>Study DGD-3-44 # of Subjects</b>
<b>Enrolled AIP All Included</b>	416 377 adults/39 peds	151
<b>Randomized and/or Received study drug</b>	402 364 adults/38 peds 283 Dotarem/119 Magnevist	150
<b>Completed study</b>	395 238 Dotarem (97.1%)/117 Magnevist (98.3%)	150
<b>Discontinued study</b>	7 (2.9%) 2 (1.7%)	2
<b>...Prior to any study drug</b>	5/7	1
<b>...Consent withdrawal</b>	1/0	2
<b>...Protocol deviation/ failed inclusion criteria</b>	1 (failed inclusion criteria)	22 (no histology); 1 received no study drug; total 23 “out of timeframe” per sponsor
<b>...Adverse event</b>	2/0	1
<b>...Lost to f/u</b>	1/0	
<b>...Other</b>	1/1	
<b>...Technical</b>	2/1	

As can be seen for both studies, there were only a small number of subjects that discontinued from either study. The protocol deviation/failed inclusion criteria for the DGD-3-44 study refers to the primary objective for this study which was to confirm the efficacy of Dotarem using a gold standard histological diagnosis.

At least one protocol deviation was reported in 31.9% of adult patients in the -050 study with a slightly higher incidence for Dotarem (34.7%) compared to Magnevist (26.1%). Major protocol deviations were reported in 7.7% of patients at a similar incidence in both arms. Several patients had more than one deviation. Major deviations included:

- Incorrect dosing to include missing volume or failure to receive injection
- Failure to complete at least 1 MRI
- Missing MRI sequences for off site reading
- Randomization errors
- Safety evaluation not performed or performed at incorrect time
- Date of consent after the date of screening

The most common minor protocol deviations included scheduled timings.

23 of the 38 pediatric AIP subjects (60.5%) in the -050 study reported at least one deviation with 7 (18.4%) having a major deviation with the majority of the major deviations either due to missing data or incorrect timing of data acquisition (scheduled timings.)

43 subjects in the DGD-3-44 trial experienced protocol violations. Most major protocol violations were secondary to the subject not fulfilling the criteria of the study which required biopsy or surgery for histology after the Dotarem exam. Most minor deviations were secondary to scheduled timings.

#### 6.1.4 Analysis of Primary Endpoint(s)

For both of the US IND studies, the primary efficacy evaluations were based on the the following three visualization variables assessed on the unenhanced and combined unenhanced and enhanced MRI:

- Degree of contrast enhancement (0=unevaluable, 1=seen, but imperfectly, 2=seen completely/perfectly)
- Assessment of border delineation (0=unevaluable, 1=seen, but imperfectly, 2=seen completely/perfectly)
- Internal morphology of lesions (0=unevaluable, 1=seen, but imperfectly, 2 =seen completely/perfectly)

Descriptive statistics were used to summarize demographic, efficacy, and safety data. Logistic regression models were used to evaluate the primary endpoint in the full analysis set (FAS-all subjects with valid co-primary endpoint assessments having unenhanced and contrast enhanced MRI exams) and the per protocol (PP-all FAS subjects without significant protocol deviations). Additional efficacy analyses were performed using data from those same subjects from the FAS who also fulfilled all major

provisions of the protocol, (PP), with subjects excluded for reasons as previously noted as protocol deviations. Using both the FAS and the PP populations, for both studies, analyses of the 3 lesion character variables (contrast enhancement, border delineation, and internal morphology) for the 3 individual readers demonstrated a statistically significant change in scores from the unenhanced to the combined unenhanced + enhanced or pre compared to pre + post images ( $P < 0.001$ ).

Secondary efficacy criteria were evaluated for the FAS using summary statistics derived from the multiple regression model for the 3 MRI modalities, the Chi squared test, and logistic regression models.

### **Conduct of the Blinded Read (Pivotal phase 3 studies):**

A prospectively planned blinded image evaluation was performed in a core laboratory by independent radiologists with expertise in interpretation of MRI of CNS diseases trained in the study design. The readers were experienced radiologists not associated with the study with no knowledge of the details of the study. Readers were responsible for the conduct of the blinded read. The core laboratory, (b) (4) was responsible for the image preparation and blinded reading planning, and for conduct for the image analysis of both phase 3 pivotal trials. Site set up, image quality control, reader training, the blinded read, collection of data, and archiving was all performed by (b) (4) for the -050 study and (b) (4) for the DGD-3-44 study. The manual included sections specifically related to image acquisition, reader training, and procedures to be carried out with regards to randomization and blinded reads to minimize recall bias and to insure that only a single image set for any patient was read in the same session. Readers received training in the protocol, operation of the work station, and the eCRF prior to the reading sessions. The blinded reading consisted of the following parts which were read in batches of 20-40 subjects separated by a wash out period of at least two weeks between evaluations: non contrasted images (pre), contrasted images (post), and paired images (pre + post). Lesion tracking (concordance) was performed as an independent off site procedure by a neuroradiologist in order to guarantee matching of lesions between modalities and between readers for the kappa (reader variability) only.

Intra reader variability assessments done as part of the final analysis were used as secondary objectives. Inter reader variability was assessed as there were three blinded readers for all the images.

Secondary criteria for evaluation included evaluation of the 3 primary efficacy variables by the on site investigators.

### **Primary Efficacy Analysis (Pivotal Phase 3 Studies):**

The primary objective of these studies was to demonstrate superiority of the combined unenhanced and Dotarem-enhanced MRI compared to unenhanced MRI for:

- Degree of contrast enhancement
- Assessment of border delineation and
- Internal morphology of lesions

The individual results for the three blinded readers graded the three variables for the five largest representative lesions using the three point scale (0-2) as previously noted. For each endpoint, a subject score was computed by adding up all lesion scores within subject for each MRI modality (i.e. per subject paired scores sum and pre scores sum—not a mean score) and then calculating within subject the difference between the two MRI modalities (paired score sum – pre score sum). Each co-primary criterion was analyzed using a multiple regression model, modeling the subject's score as a function of the MRI modality (pre and paired) with adjustment on centers and repeated measures for the subject. To be successful, 2 out of 3 readers had to meet the alternative hypothesis. The lesion characterization variables (contrast enhancement, border delineation, and internal morphology) were tested for the superiority of Dotarem-enhanced MRI versus unenhanced MRI using regression models for a single group with 0.025 one sided confidence interval. Null and alternative hypotheses were as follows:

$H_0$ : combined unenhanced and Dotarem mean = unenhanced MRI mean versus  
 $H_1$ : combined unenhanced and Dotarem mean  $\neq$  unenhanced MRI mean

The study was to be considered successful if 2 out of the 3 readers simultaneously met the alternative hypothesis ( $\mu_1 > \mu_0$ ;  $1-\beta = 0.80$  in the Dotarem group with a statistically significant ( $p \leq 0.025$ ) positive mean score per patient for all 3 co-primary endpoints.

All efficacy values for study -050 were evaluated in similar fashion for both Dotarem and Magnevist with comparison as a secondary analysis.

Efficacy analyses were performed for the full analysis set (FAS) and for the per protocol set (PPS). The FAS was comprised of data from all subjects for whom images and entries on case report forms were available for unenhanced and combined unenhanced and Dotarem-enhanced MRI. The PPS was comprised of all subjects who also fulfilled all major provisions of the protocol with subjects excluded for major protocol deviations. For the -050 study, there was a difference of 11 subjects between the FAS and the PPS, N = 393 and N = 382 respectively. For study DGD-3-44, there was a difference of 25 subjects however for the re-read, 150 image sets were submitted for the re-read and 149 image sets were read. Results of the efficacy analyses performed for both the FAS and PPS were similar.

For both the -050 and -051 studies, the changes in scores from pre-contrast to post contrast were found to be statistically significant for all 3 individual readers (P<0.0001 in all cases) for the three lesion characteristic variables.

As seen in Table 13, for study -050 mean contrast enhancement score increased from almost zero pre-contrast to about 2.53 post contrast, mean border delineation increased by 1-1.5 points, and mean internal morphology increased by 1.5 to 2.75 points.

Analysis of study -051 revealed mean contrast enhancement score increases of 2 points or greater, mean border delineation score increases of about 1 point and slightly greater increases than border delineation scores for the mean internal morphology scores.

The differences in scoring (points) are accounted for by the number of lesions with more subjects in the -051 study having a single lesion.

**Table 13: Study DGD-44-050 Summary of Lesion Visualization Variables- Combined Unenhanced/Dotarem-Enhanced vs. Unenhanced, (FAS, N = 278)\***

Reader	Lesion Contrast Enhancement Score (Estimate/Mean)	Lesion Border Delineation Score (Mean)	Lesion Internal Morphology Score (Mean)
Reader 1	Unenhanced 0.05/0.01 Combined 3.18/3.11 Difference 3.13	Unenhanced 1.09/1.06 Combined 3.35/3.30 Difference 2.26	Unenhanced 0.97/0.97 Combined 3.72/3.70 Difference 2.75
Reader 2	Unenhanced 0.05/0.01 Combined 3.81/3.73 Difference 3.76	Unenhanced 1.65/1.62 Combined 4.57/4.49 Difference 2.92	Unenhanced 1.80/1.76 Combined 4.57/4.49 Difference 2.77
Reader 3	Unenhanced 0.02/0.01 Combined 3.01/2.95 Difference 2.99	Unenhanced 1.43/1.43 Combined 2.58/2.54 Difference 1.15	Unenhanced 1.42/1.45 Combined 2.96/2.93 Difference 1.54

\* Estimate used for variation (difference); mean values were similar

**Table 14: Study DGD-44-051 Summary of Lesion Visualization Variables- Combined Unenhanced/Dotarem-Enhanced vs. Unenhanced, (FAS, N = 149)\***

Reader	Lesion Contrast Enhancement Score (Mean)	Lesion Border Delineation Score (Mean)	Lesion Internal Morphology Score (Mean)
Reader 1	Unenhanced 0.00 Combined 2.06 Difference 2.06	Unenhanced 0.94 Combined 1.98 Difference 1.04	Unenhanced 1.09 Combined 2.23 Difference 1.14

	CI (1.90, 2.22)	CI (0.88, 1.21))	CI (1.00, 1.29)
Reader 2	Unenhanced 0.00 Combined 2.11 Difference 2.11 CI (1.91, 2.29)	Unenhanced 1.41 Combined 2.18 Difference 0.77 CI (0.62, 0.92)	Unenhanced 1.34 Combined 2.28 Difference 0.94 CI (0.80, 1.08)
Reader 3	Unenhanced 0.00 Combined 2.21 Difference 2.21 CI (2.02, 2.40)	Unenhanced 0.34 Combined 1.62 Difference 1.28 CI (1.07, 1.48)	Unenhanced 0.67 Combined 2.41 Difference 1.74 CI (1.56, 1.92)

\* Mean score used, Confidence Intervals (CI) for the difference are 95%

As has already been noted, for each variable the patient score was computed by summing all lesion scores within subject for each MRI modality (i.e., per subject combined or pre + post sum and pre sum alone) and then calculating the within subject difference between the two modalities, (noted as "Difference" in the tables above). For both studies, all visualization outcomes achieved statistical success for all 3 readers with p value <0.001.

*Reviewer's Comment: Readers' scores for the unenhanced images (pre Dotarem), the combined images (pre Dotarem images + post Dotarem images), as well as the difference between the two scores are higher for the -050 study. This is secondary to study entry criteria (3 lesions maximum for the -051 study) with 75% of subjects in the -051 study presenting with only a single lesion.*

**Pediatric Supportive Efficacy Analyses (DGD-3-15, DGD-3-16, DGD-3-49, DGD-44-050):**

In addition to the inclusion of 38 pediatric subjects ages 2-17 years in the -050 study, the applicant conducted three studies in the pediatric population ages newborn through 17 years for a total of 137 subjects. There were a total of 99 subjects in the three studies (7 subjects age 17 years, thus 92 up to age 17 using the current FDA age group and in line with the -050 study). 33 subjects were ages 2-5 years, 57 were 6-11 years, and 40 were 12-17 years.

The applicant cites additional post marketing studies and PSUR data as supportive for the pediatric indication. The applicant requested a priority review based on a proposed indication for the pediatric population under age 2 years. For the population under age 2 years, the applicant noted 7 subjects age < 2 years in the three pediatric clinical trials and additional controlled studies and data to include a 7 ½ year observational post marketing study that included 10 subjects < 2 years, PSUR data from 3-89 to 3-31-12 that included 8 subjects <2 years (0.5% of population), and 4 smaller postmarketing

studies that included pediatric subjects of all ages as well as adults. The majority of pediatric subjects in the post marketing studies were evaluated for a CNS indication.

For consideration of CNS efficacy, as a general statement, the applicant noted that 70% of pediatric tumors are posterior fossa, 30% in the hemispheres.

Study 3-15, conducted in 1988 enrolled 29 for efficacy with safety evaluation of obtained laboratory parameters for 20 of these, generally at baseline then at 2 and 24 hours although not all labs reported for all 20 subjects. All subjects were evaluated for efficacy however only 2 subjects in the under age 2 years group had laboratory evaluations.

For all 29 subjects, post injection diagnosis was rated as complementary or better in 69% of cases with modified treatment strategy overall in 34% of cases. For intraxial tumors diagnosis could be helped for vascular tumors such as ependymoma however overall with contrast 36% were less good, 14% were identical, with 29% deemed better and 21% complementary and treatment modification was done in only 2/14 (14%) of cases. For extraxial tumors, visualization with contrast was better (86%) or complementary (14%) and 4/7 (57%) had treatment modification post contrast. For intramedullary tumors there was identical visualization for 14%, better visualization for 62%, and complementary visualization for 13% with treatment modification for 10/29 (34%). Examples of efficacy with treatment modification included subject 19 who had a meningioma with decision to embolize rather than surgically remove, subject 21 had an abscess, no change with contrast and no change in treatment and subject 16 had a diagnosis of flaccid paraplegia with a normal scan. These findings are summarized in Table 15.

**Table 15: Efficacy Results, Diagnosis and Treatment Modification Post Vs Pre Contrast, DGD-3-15, N = 29, 0.1-17.0 Years**

Disease	Diagnosis Post Contrast Vs Pre Contrast				Treatment Modified After Contrast
	Less Good	Identical	Better	Complementary	
Intra-axial Cranial	5 (36%)	2 (14%)	4 (29%)	3 (21%)	2/14 (14%)
Extra-axial Cranial	0 (0%)	0 (0%)	6 (86%)	1 (14 %)	4/7 (57%)
Intra-medullary	0 (0%)	2 (25%)	5 (62%)	1 (13%)	4/8 (50%)
Total Cases and % of Cases	5 (17%)	4 (14%)	15 (52%)	5 (17%)	10/29 (34%)

Study 3-16, conducted in 1988 enrolled 20 for efficacy with safety assessments for AEs only. The study report noted 4 cases with protocol deviations related to MRI sequences or to missing data of not doing a pre-contrast exam thus Table 16 below accounts for only 19 subjects. 2 subjects under age 2 years were included in the study.

As noted in Table 16 below, most tumors studied were intra-axial but treatment was not modified after contrast. There were insufficient numbers to conclude for extra-axial and intra-medullary tumors although for the total number of cases, there was a low percentage of treatment modifications post scan. Overall subject numbers are insufficient to draw extensive conclusions regarding efficacy in the overall age group as well as in the under 2 age group (specific diagnoses per subject not specified in the study report).

**Table 16: Efficacy Results, Diagnosis and Treatment Modification Post Vs Pre Contrast, DGD-3-16, N = 19**

Disease	Diagnosis Post Contrast Vs Pre Contrast				Treatment Modified After Contrast
	Less Good	Identical	Better	Complementary	
Intra-axial Cranial	0 (0%)	0 (0%)	6 (40%)	9 (60%)	0/15 (0%)
Extra-axial Cranial	0 (0%)	0 (0%)	1 (50%)	1 (50 %)	1/2 (50%)
Intra-medullary	0 (0%)	1 (50%)	1 (50%)	0 (0%)	1/2 (50%)
Total Cases and % of Cases	0 (0%)	1 (5%)	8 (42%)	10 (53%)	2/19 (11%)

Study 3-29, conducted in 1990-91 enrolled 50 children for efficacy with safety assessments for AEs up to 45 minutes post dose only. There were 2 subjects under age 2 years.

For efficacy evaluation, suspected pathology was intra-axial for 33/49 (67%-1 case not specified), spinal for 15/49 (31%), and combined for 1/49 (2%). 42% of exams were for diagnostic confirmation, 26% were for routine control, and 10% were for post op control. Lesion delineation (assessed as yes/no) was yes for 21/27. 12/14 that had cystic or necrotic components were better defined. Additional information was obtained for 20-40% of patients for anatomic features such as the size of the tumor, type of lesion, or localization of the tumor. 80% had no change in diagnosis but diagnosis was more

precise. 4% had an unchanged diagnosis with no additional information. 16% had modified diagnosis. The study report provided the details of the efficacy analysis/change as follows: for 8 with diagnosis modified post contrast, a 17 yo had tumor ruled out (malformation dx), a 6 yo had recurrent tumor ruled out post resection, a 12 yo had a normal exam (ruling out leukemic infiltrate), a 4yo had recurrent tumor while on chemotherapy, a 15 yo had a different type of tumor than suspect with hemorrhage masking the findings pre contrast, a 4 yo had a firm diagnosis (not the suspected diagnosis of tumor extension), a 2 yo had residual rather than recurrent tumor, and a 10yo had the type of pituitary tumor established. The overall conclusion in the study report regarding diagnosis modification was that the use of contrast was of benefit for diagnosis modification with more precise diagnosis/modified diagnosis in 96% of children studied. For this, the report cited 5 cases with treatment modification that included a 6 yo with a more precise diagnosis and confirmation of suspected tumor recurrence, a 7 yo with a more precise diagnosis leading to treatment modification, a 12 yo (mentioned previously) with a normal exam, a 6 year old with confirmed meningeal metastases, and a 7 yo where suspected recurrence was confirmed. The overall conclusion by the investigator regarding therapeutic approach was that contrast facilitated therapeutic decision making in 48/50 (96%) of cases including the 5 above cases where treatment was modified and 23 cases where the decision not to initiate treatment was reinforced. The impact of Dotarem is summarized in Table 17 below.

**Table 17: Impact of Dotarem ®; Pre-Contrast Vs Post Contrast Diagnosis and Therapeutic Approach, DGD-29, N = 50**

<b>Diagnosis/Therapeutic Approach Pre-Contrast vs Post-Contrast MRI</b>	<b>n</b>	<b>%</b>
Unchanged diagnosis with no additional information	2	4.0
Unchanged diagnosis but more precise	40	80.0
Modified diagnosis	8	16.0
Established diagnosis total number	49	98
Choice of initial treatment approach	6	12.5
Modification of treatment approach	5	10.2
Continuation of treatment approach	15	30.6
Decision not to initiate treatment	23	46.9
Facilitated therapeutic decision making total number	48	96

38 pediatric subjects ages 2-17 years were enrolled in the -050 study as additional supportive study for the pediatric indication. The same clinical methodology and clinical assessments were used for these subjects as for the adults enrolled in this same study apart from a single treatment arm only and analysis using descriptive statistics. This study included 22 female (57.9%) subjects and 16 male (42.1%) subjects ranging in age from 2.9 to 17.3 years with an average age of 9.29 years. 68.4% were Caucasian. 23.7% were Black. 7.9% were classified as Other. The

number of subjects evaluated per reader for pre, post, and paired images ranged from 31 to 36. Mean scores were calculated for each of the three variables—border delineation, internal morphology, and contrast enhancement. Although results for reader 2 were consistently higher for the paired image set than for the other two readers, the scores for the paired images and for the post images were greater than scores for the pre images for all readers. Readers' scores generally supported improved lesion visualization with contrast and subjective improvement in image quality and diagnostic confidence. The number of lesions visualized before (pre) and after (post) contrast did not differ. When mean percent enhancement was evaluated, 2 of 3 readers noted relatively high values (73% and 81%) with one reader noting a lower value (42%) although contrast to noise ration improved for all three readers post contrast. Using Kappa Coefficient scores, there was moderate intra reader variability for all three lesion variables and poor inter reader variability for border delineation and internal morphology with moderate variability for contrast enhancement.

*Reviewer's Comments:*

- 1. Both the -050 and the -051 re read study were successful in achieving the three co- primary endpoints of superiority of the three lesion visualization parameters using paired (uncontrasted + contrasted) images versus pre (uncontrasted) images at a p value <0.001.*
- 2. This reviewer does not recommend approval for the under 2 years age group based on insufficient numbers (7) and insufficient safety evaluations for this population in the clinical trial setting to be further discussed in Section 7 of this review.*
- 3. This reviewer noted ethnicity of the pediatric subjects in the -050 trial to be reflective of the proposed US population even though the three dedicated pediatric clinical trials reflected no diversity. As such, this reviewer considers this supportive of pediatric efficacy.*
- 4. This reviewer noted that although inter reader variability was poor for lesion border delineation and internal morphology, percent lesion enhancement was relatively low for one of the three readers, and the number of lesions did not differ between uncontrasted and contrasted images or paired images, the majority of endpoints assessed favored paired or contrasted images for evaluation compared to non contrasted images.*

#### 6.1.5 Analysis of Secondary Endpoints(s)

The secondary criteria for evaluation of the -050 and -051 studies were as follows:

- Lesion visualization, 3-point scale, lesion level
- Lesion number and location
- Image quality, 3 point scale
- Level of diagnostic confidence, 5 point scale
- Signal intensity
- Inter and intra reader agreement'

Additional secondary criteria of the -050 study were:

- Comparison of Dotarem enhanced MRI to Magnevist MRI in terms of lesion visualization, lesion number and location, image quality, diagnostic confidence, and signal intensity
- Comparison of Dotarem to Magnevist for various safety parameters including a subset comparing ECG recordings
- Safety and efficacy of Dotarem in a pediatric population.

For the -051 study, the impact on patient therapeutic management based on image evaluation was also evaluated.

Most of the primary and secondary variables were also assessed by the investigators and were considered as secondary analyses.

Analyses of these secondary endpoint variables in the adult population will be discussed in greater detail.

Analysis of the three visualization parameters for Magnevist revealed similar scores to the Dotarem parameters for the contrast enhancement, border delineation, and internal morphology. Significant differences ( $p < 0.001$ ) were observed for Magnevist for all three variables and there was no statistically significant difference between the Dotarem and Magnevist results supporting the validity of the Dotarem study. Similar results were achieved for comparison of the post versus pre images generally for 2 of the 3 readers for both drugs. Table 18 below presents the Magnevist scores for the variables with the Dotarem score (as a difference) for comparison.

**Table 18: Magnevist Versus Dotarem Comparison of Primary Efficacy Variables**

Reader	Image Set	No. of Subjects	Mean Contrast Enhancement	Mean Border Delineation	Mean Internal Morphology
1	Pre	111	0	1.19	1.09
1	Paired	114	3.39	3.60	3.96
1	Difference Magnevist		3.38	2.38	2.86
1	Difference Dotarem		3.13	2.26	2.75
2	Pre	113	0	1.55	1.71
2	Paired	114	3.73	4.47	4.48
2	Difference Magnevist		3.71	2.91	2.76
2	Difference Dotarem		3.76	2.92	2.77
3	Gadobutrol	113	0	1.65	1.49
3	Gadoteridol	116	3.13	2.88	3.09
3	Difference Magnevist		3.15	1.24	1.62
3	Difference Dotarem	315	2.99	1.15	1.54

For the Dotarem and Magnevist comparison, when lesion variables were assessed independently on a three point scale, the paired images were superior to the pre images alone, both for Dotarem and Magnevist, and in most cases the difference was statistically significant. For the -051 study, superiority of the individual lesion variables was statistically significant both on comparison of the paired and the post images to the pre images. Subjective comparison (better/worse) generally favored the paired and post images and was similar for Dotarem and Magnevist. For the -050 study, the mean number of lesions detected was slightly higher for the paired images for both Dotarem and Magnevist and lesion numbers for Magnevist were generally higher than for Dotarem with no differences in the numbers of lesions for the -051 study because all subjects in the study presented with relatively large tumors.

For the subjective evaluation of image quality, readers generally recorded higher scores for both the Dotarem and Magnevist contrasted images for the -050 study with variable scores for the -051 study. Mean scores for diagnostic confidence were also higher for the contrasted Dotarem and Magnevist images again with variable scores for the -051 study.

For the -050 study, signal intensity calculations for mean percentage enhancement were moderate for 2 of the 3 readers for both contrast agents, less in both arms for the third reader and there were significant increases in the contrast to noise ratio for all readers for both contrast agents. For the -051 study, percentage lesion enhancement

was variable among the three readers with contrast to noise ratios significantly better for all three readers.

Kappa coefficients were evaluated on a scale of poor (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80), and very good (0.81-1.00). Kappa coefficients for intra reader agreement in the -050 study ranged from poor to fair to moderate and were generally poor for internal morphology. Inter reader agreement was generally poor for all modalities and for all reader combinations apart from contrast enhancement which was considered moderate for the paired images and fair for the post images. For the -051 study, most comparisons showed either poor or moderate intra reader agreement. The conclusion from the inter reader comparison was that agreement was mostly poor or fair but that agreement was better for paired images than for the pre images.

Lastly, for study -051 each of the blinded readers was asked to assess whether administration of Dotarem would alter the therapeutic management of a subject from that which would have occurred based on prior non-enhanced MRI for that same subject. There was no significant difference in therapeutic management for two out of three readers.

*Reviewer's Comments:*

- 1. Secondary evaluation criteria are generally supportive of efficacy although there was more variability for the -051 study.*
- 2. Comparisons with Magnevist for the adult population generally yielded similar results.*
- 3. Intra and inter reader agreement are generally poor or fair with some moderate agreements noted when Kappa coefficients were used, with lesser agreement for the -051 study.*
- 4. The number of lesions detected did not improve significantly with contrast for either study and it was noted that the subjects in the -051 study presented with relatively large tumors. Furthermore, for 2 of the 3 readers, there was no statistical difference in therapeutic management comparing the -051 contrasted with non contrasted images. As such, this reviewer considers this study may not be an adequate representation of the intended population/proposed indication.*

### 6.1.6 Other Endpoints

Additional endpoints have previously been discussed above (secondary endpoints) and are also discussed in the review of the pediatric studies. As already noted, these are generally supportive of the proposed indication for the -050 study. However, this reviewer has noted limitations of the -051 re read study.

Results of investigators' analyses were generally similar to those of the blinded readers.

### Subpopulations

#### Comparison and Analyses of Results Across Studies and in Subpopulations:

Key demographic variables for the two US phase 3 studies and for are summarized in the table below.

**Table 19: DGD-44-050 & DGD-44-051: Demographic Variables**

		<b>Study DGD-44-050 Dotarem N = 245</b>	<b>Study DGD-44-051 N = 151</b>	<b>Study DGD-44-050 Magnevist N = 119</b>
<b>Sex</b>	Male	114 (46.5%)	84 (55.6%)	54 (45.4%)
	Female	131 (53.5%)	67 (44.4%)	65 (54.6%)
<b>Age</b>	Mean	53.2	53.9	55.9
	Min, Max	18.8, 85.1	18.0, 79.0	19.0, 94.4
<b>Race</b>	Caucasian	204 (84.5%)	147 (07.4%)	95 (79.8%)
	Black	9 (3.7%)	1 (0.7%)	8 (6.7%)
	Asian	27 (11.0%)	97 (28.95)	15 (12.6%)
	Other	2 (0.8%)	3 (2.0%)	18 (5.6%)
<b>Weight</b>	Mean	76.0 kg	73.2 kg	76.7 kg
	Min, Max	43.0 kg, 136.0 kg	41.0 kg, 120.0 kg	44.0 kg, 135.4 kg

<b>Region</b>	US, Europe, Latin America, South Korea	Europe (8 sites in France, 1 site in Germany)	US, Europe, Latin America, South Korea
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For the -050 study, adequate comparability of the Dotarem and Magnevist cohort can be concluded with regards to their subjects' demography.

- For both drugs, slightly more females than males were included.
- The mean age and age range was similar for both groups.
- The racial distribution of subjects was compatible with the region of study recruitment.

For the -051 study, the ethnicity (Caucasian) was a reflection of the study sites with 8/9 sites in France and 147/150 subjects classified as Caucasian.

The applicant performed analyses of each co-primary lesion variable by gender, ethnicity, and geographic region. For all three variables for the Black population, the difference between the pre and paired scores was greater for Magnevist than for Dotarem. Otherwise, general consistency was noted for the scores between the groups that were stratified.

*Reviewer's Comment: Even though the drug product is for diagnostic use (as versus therapeutic use), this reviewer considers the ethnicity demographics as skewed and not representative of the intended population. In particular, tumoral disease only was evaluated which does not reflect the spectrum of diseases for which this product is intended and other disease categories may be more common in other ethnic groups, for example inflammation/infection.*

#### Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant did not conduct any dose ranging studies to provide information relevant for dosing recommendations however, as described below, PK studies were conducted in healthy volunteers and a limited study was conducted in subjects with renal impairment. The PK studies did not include any studies using placebo (saline) injection.

#### Special Populations

The applicant conducted 4 PK studies in adult humans comprised of 1 study to evaluate safety and PK after single administration of Dotarem, 1 study to evaluate safety and PK of Dotarem after single and triple dose injections, 1 study to evaluate safety and PK of Dotarem in normal subjects and in subjects with renal failure, and one study to evaluate

safety and PK (in particular electrocardiographic safety) in subjects receiving a triple dose of Dotarem. PK studies evaluated the effects of endogenous factors such as age and body weight based on pooled data consisting of all phase 1 studies in healthy adults. No studies were conducted to assess placebo versus Dotarem.

Study DGD 3-6 was conducted in 6 healthy male volunteers ages 20-29 for PK determination using blood, urine, and feces collections up to 48 hours post dose. Vital signs were recorded during the course of the study. The data were consistent with a two compartment model in which the intravenously administered dose was rapidly distributed between a central and peripheral compartment (passive extravascular diffusion in the interstitial space) and was then eliminated primarily in urine by glomerular filtration with a small amount of fecal excretion (less than 0.002%). The volume of distribution at equilibrium suggested test material distribution in extracellular water. Two subjects noted mild adverse effects described in the study report as irritation of the eyes and throat with slight edema of one eyelid for one subject and transient sensation of suffocation for another subject.

The primary objective of study DGD-48 was to calculate PK parameters of Dotarem after 0.1 mmol/kg injection in a group of healthy volunteers ages 18-45 and to calculate similar parameters in a second group that received a second injection of 0.2 mmol/kg after 20 minutes. Follow up was up to 48 hours. In the first group, there were differences in drug distribution attributed to higher body weight in men. Apart from this, the results of the study showed that exposure is dose proportional. 73-85% of the dose was recovered in urine over the 48 hour interval. Laboratory tests and vital signs were unremarkable. Four AEs were noted.

A thorough QT study was performed including PK. 40 subjects received an 0.1 mmol/kg dose of Dotarem followed by a second dose of 0.2 mmol/kg 20 minutes later. Eleven ECGs were recorded for each subject for each period. The central tendency analysis on absolute values and changes from baseline value of QT and/or QTc measured at numerous time points during the study showed no difference between active treatment and placebo. Results of the statistical analysis showed that Dotarem administration did not result in prolongation of QT or QTc intervals by more than 5 ms compared to placebo when analyzing maximal increases. Analysis of the AUC for both treatments confirmed this. Results of the analysis of outliers confirmed this. No QT or QTc value above 480 ms and no QT or QTc increase above 60 ms was observed after either treatment. No increase in QT or QTcF greater than 30 ms was observed after Dotarem administration. 6 patients had QT and QTc values greater than 450 ms, 3 under both treatments and 3 under Dotarem only. These occurred as isolated occurrences. 7 patients (4 under placebo, 3 under Dotarem) had QTcB increases above 30 ms. No clinically significant abnormalities were noted on other ECG parameters, (heart rate, PR, QRS, T and U waves, 24 hour Holter recordings). 7 of the 40 patients reported adverse events that were mild to moderate in intensity, most

frequently headache. There were no clinically significant abnormalities in the laboratory safety parameters or in vital signs. No definite cardiac signals were noted.

Study DGD-3-28 was a study in patients with chronic renal failure with comparison control to a population of healthy subjects. 12 patients were equally distributed in three groups of different stages of renal impairment or into a normal group as defined by serum creatinine clearance: (1) moderate impairment of creatinine clearance, (clearance <60 and >30 mL/min); (2) severe impairment (clearance <30 mL/min and > 10 mL/min) and; (3) normal renal function. Patients received an 0.1 mmol/kg bw dose of Dotarem. Blood and urine PK parameters were evaluated before and after injection for 24 hours in the healthy subjects, for 48 hours in subjects with moderate impairment, and for 72 hours in subjects with severe impairment. The mean half life was 1.62 hours in normal subjects, 5.05 hours in subjects with moderate renal failure, and 13.9 hours in subjects with severe renal failure. Laboratory safety parameters were reported as satisfactory with no AEs reported. The overall conclusion was that decreased clearance of Dotarem was associated with increasing renal impairment.

The applicant did not conduct any hepatic impairment studies.

*Reviewer's Comments:*

- 1. The Applicant did not conduct any studies to assess drug versus placebo (saline).*
- 2. The Applicant conducted only a limited study in subjects with renal impairment and did not assess dialysability in humans. This reviewer concludes that, although efficacious, Dotarem should be used with caution in renally impaired patients.*

Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and/or tolerance effects are not applicable to Dotarem, a single dose imaging compound.

6.1.10 Additional Efficacy Issues/Analyses

None. See reviewer's comments regarding particular efficacy issues in both adult and pediatric populations.

**Overall reviewer comment regarding efficacy:**

*When evaluating the entire efficacy profile of this product, this reviewer recommends approval for the adult population abased on a single phase 3 pivotal trial with supportive a supportive re-read study. Approval in the pediatric population ages 2-17 is recommended based on demonstration of efficacy and comprehensive safety monitoring during the clinical trial. Approval for pediatric patients under age 2 is not recommended.*

*1. For the phase 3 pivotal SPA study DGD-44-050 using Magnevist as a comparator in the adult population, when unenhanced images were compared to combined unenhanced + Dotarem-enhanced images, the applicant met the primary endpoint of superiority of the combined image set for 3 visualization variables, (contrast enhancement, border delineation), as based on a pre-specified statistical analysis plan. Most secondary endpoints, in particular comparison to Magnevist and use in the pediatric population ages 2-17 years were also supportive and there was no statistically significant difference between Dotarem and Magnevist for the three co-primary variables, although for the Black population, Magnevist had larger differences between pre and paired scores. Many Kappa Coefficients for intra and inter reader agreement were poor.*

*2. For the phase 3 pivotal re-read study DGD-44-051, the applicant met the primary endpoint of superiority for all three lesion variables. Supportive results for this study were variable, although some were statistically significantly for some endpoints and for some readers. The number of lesions between pre to paired images was not different based on large tumor size and the large percent having single lesions, (75%) and intra and inter agreement using Kappa Coefficients was only poor to fair for most variables for most readers. Additionally, 2 of the 3 readers observed no statistically significant difference in therapeutic management decisions comparing contrasted images to unenhanced images. This reviewer felt that other factors of this study are not representative of the intended population. Enrollment was limited to subjects with known tumoral disease, mostly single lesions, which were only for the brain. 8 out of 9 sites were in a single country, (France), with Caucasians accounting for greater than 97% of the population studied.*

*3. The number of subjects ages 0-23 months enrolled in the pediatric studies was insufficient to conclude efficacy ( or safety) in this population, even though this reviewer acknowledges that according to study reports, Dotarem made a positive contribution to diagnosis even though changes in therapeutic management were variable. These studies were also conducted in a single country at single centers allowing for the*

*possibility of investigator bias. As will be further discussed in the safety section, safety parameters were not adequate to recommend approval.*

*4. Regarding the pediatric population of all ages, the applicant did not conduct any juvenile P/T studies or any PK studies to support dose and efficacy in children.*

*5. Adult PK studies were limited. There were no phase 1 studies comparing Dotarem to placebo. Special population studies were limited to study of 8 subjects with renal impairment conducted as a PK study.*

*5. No dose ranging studies were conducted.*

## **7 Review of Safety**

### **Safety Summary**

The Integrated Summary of Safety presented by the applicant considered all PK and phase 2-4 studies in which subjects received Dotarem injection, regardless of concentration, including studies in which subjects received a comparator GBCA, (Magnevist or Gadovist). The applicant did not conduct any PK studies using placebo (saline). The total number of studies, the number of subjects enrolled and treated, and the number of subject treatments considered in the summary is reflected in Table 20. Safety analyses were performed for three pools: the 49 clinical studies that were conducted for various indications, to include the PK studies, 23 clinical studies for the proposed CNS indication, and the two pivotal CNS studies.

**Table 20: Number of Studies, Subjects Enrolled, Subject Treatments by Phase\***

<b>Study Phase</b>	<b>Number of Studies</b>	<b>Subjects Enrolled and Treated</b>
PK studies (no placebo)	3	50
<b>Total phase 1</b>	<b>3</b>	<b>50</b>
<b>Dotarem</b>		
Phase 2	13	336
Phase 3	26	
Phase 4	7	359
<b>Total</b>	<b>43</b>	<b>2813</b>
<b>Dotarem/Comparator</b>		
Phase 2	1	20
Phase 3	2	693
Phase 4	2	204
<b>Total</b>	<b>5</b>	<b>917</b>
<b>Total Comparator</b>	<b>5</b>	<b>371</b>
<b>Dotarem CNS Indication</b>		
Phase 2	11	276
Phase 3	11	1003
Phase 4	1	50
<b>Total</b>	<b>23</b>	<b>1329</b>
<b>Dotarem Body Indication</b>		
Phase 2	1	20
Phase 3	6	402
<b>Total</b>	<b>7</b>	<b>422</b>
<b>Dotarem MRA Indication</b>		
Phase 3	8	653
Phase 4	5	239
<b>Total</b>	<b>13</b>	<b>892</b>
<b>Dotarem Special Safety</b>		
Phase 2	1	40
Phase 3	1	20
Phase 4	1	70
<b>Total</b>	<b>3</b>	<b>130</b>

\* Numbers vary from ISS Clinical Development Summary based on special population group

**141 pediatric subjects were enrolled in clinical trials, 7 < age 2 years, 123 ages 2-16, and 11 ages 16-17. For the -050 study, there were 36 subjects ages 2-16 and 2 subjects age 16-17.**

**Table 21 is a summary overview of all clinical studies for Dotarem safety in various indications and forms the basis for the safety review.**

**Table 21: Overview of Clinical Studies for Dotarem Safety in Various Indications**

<b>Study # Study year Study sites location(s )</b>	<b>Subject Age Range (yrs); Total # Subjects; # Subjects exposed toStudy Drug</b>	<b>Study Phase</b>	<b>Study drug Dosage (route: Intravenous)</b>	<b>Study Indication or Type of Study</b>
DGD-3-6; 1987; UK	21-29; 6; 6	1	0.1 mmol/kg	PK(healthy volunteers)
DGD-3-28; 1990; France	20-59; 12; 12	1	0.1 mmol/kg	PK(healthy volunteers)
DGD-3-48; 2004; France	18-45; 32; 32	1	0.1 mmol/kg+ 0.2 mmol/kg	PK(healthy volunteers)
DGD-44-39; 2004; France	19-75; 40; 40	2	0.3 mmol/kg	QT study
DGD-3-17; 1988; France	18-77; 20; 10	2	0.1 mmol/kg	CNS
DGD-3-31; 1988; France, Belgium, Switzerland	18-79; 299; 149	3/4	0.1 mmol/kg	CNS
DGD-3-7; 1987 France	18-82; 56; 56	2	0.1 mmol/kg	CNS
DGD-3-11; 1987; France	24-76; 19; 19	2	0.1 mmol/kg	CNS
DGD-3-4; 1987; France	17-72; 20; 20	2	0.1 mmol/kg	CNS
DGD-3-8; 1987; France	20-72; 54; 54	3	0.1 mmol/kg	CNS
DGD-3-1; 1987; France	21-66; 10; 10	2	0.1 mmol/kg	CNS
DGD-3-12; 1987; France	18-76; 50; 50	2	0.1 mmol/kg	CNS
DGD-3-14; 1987; France	18-70; 55; 55	3	0.1 mmol/kg	CNS
DGD-3-12; 1987 France	18-76; 50; 50	2	0.1 mmol/kg	CNS
DGD-3-5; 1987; Belgium	18-74; 10; 10	2	0.1 mmol/kg	CNS

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DGD-3-9; 1988; Belgium	25-75; 22; 22	2	0.1 mmol/kg	CNS
DGD-3-3; 1988; France	21-75; 30; 30	2	0.1 mmol/kg	CNS
DGD-3-21; 1988; France	16-80; 50; 50	3	0.1 mmol/kg	CNS
DGD-3-20; 1988; France	24-72; 48; 48	3	0.1 mmol/kg	CNS
DGD-3-33; 1994; France, Belgium	21-81; 65; 65	3	0.3 mmol/kg	CNS
DGD-3-34; 1994; France, Switzerland	20-82; 45; 45	2/3	0.3 mmol/kg	CNS
DGD-3-40; 1999; France, Belgium, Switzerland, Luxembourg	54-88; 59; 59	4	0.2 mmol/kg	CNS
DGD-3-44; 2003; France, Germany	18-79; 151; 150	3	0.1 mmol/kg	CNS
DGD-3-15; 1988; France	0.04-17; 29; 29	2	0.1 mmol/kg	CNS
DGD-3-16; 1988; France	0.5-17; 20; 20	2	0.1 mmol/kg	CNS
DGD-3-29; 1991; France	1-17; 50; 50	4	0.1 mmol/kg	CNS
DGD-44-50; 2011; USA, Latin America, Europe, South Korea	3-95; 402; 278	3	0.1 mmol/kg	CNS
DGD-3-2; 1987; France	21-76; 20; 20	2	0.1 mmol/kg	Whole Body
DGD-3-13; 1987; France	35-73; 30; 30	3	0.1 mmol/kg	Whole Body
DGD-3-19; 1987; France	20-84; 39; 39	3	0.1 mmol/kg	Whole Body
DGD-3-22; 1988; France	21-79; 24; 24	3	0.1 mmol/kg	Whole Body
DGD-3-26; 1989; France	28-85; 20; 10	4	0.1 mmol/kg	Whole Body
DGD-3-32; 1994; France, Belgium	37-77; 80; 80	3	0.1 mmol/kg	Whole Body
DGD-3-49; France, Belgium	18-87; 120; 120	3	0.1 mmol/kg	Whole Body
DGD-3-50; France	26-87; 110; 109	3	0.1 mmol/kg	Whole Body
DGD-44-44; 2008 France, Belgium, Italy, Spain	22-92; 114; 70	4	0.1 mmol/kg	Whole Body (Renal Safety)
DGD-3-36; 1998; France	24-84; 41; 41	3	0.1 mmol/kg	MRA
DGD-3-37; 1998; France, Austria	27-89; 35; 35	3	0.05 or 0.1 mmol/kg	MRA
DGD-3-38; 1998; Switzerland, Belgium	55-81; 40; 40	3	0.1 mmol/kg	MRA

DGD-3-39; 1998; France, Austria	35-84; 40; 40	3	0.05 or 0.1 mmol/kg	MRA
DGD-3-42; 2004; The Netherlands	31-72; 6; 6	4	0.125 or 0.250 mmol/kg	MRA
DGD-44-38; 2006; USA	25-87; 100; 100	3	0.1 mmol/kg	MRA
DGD-44-42; 2008; South Korea	21-86; 92; 92	4	0.1 mmol/kg	MRA
DGD-44-46; 2009; USA	23-85; 33; 33	3	0.1 mmol/kg	MRA
DGD-44-47; 2009; USA, Canada	26-80; 13; 13	3	0.1 mmol/kg	MRA
DGD-44-48; 2009; USA, Columbia, Argentina, Mexico, South Korea, Chile	20-97; 222; 222	3/4	0.1 mmol/kg	MRA
DGD-44-49; 2009; USA, South Africa, Argentina, Mexico, South Korea, Chile	21-87; 211; 211	3/4	0.1 mmol/kg	MRA
DGD-44-45; 2010; Austria, Germany, France, Italy, Spain	24-91; 189; 92	3/4	0.1 mmol/kg	MRA
DGD-44-52; 2009; Germany	45-77; 20; 20	4	0.1 mmol/kg	MRA
<b>Total Subjects exposed to Dotarem = 2813</b>				

**The data for adverse drug reactions for the studies reflects the exposure of Dotarem in all 2813 subjects in the 49 studies noted in Table 21 above, (2672 adults and 141 children aged 1.2 months to 18 years), who received a dose from <0.01 to >0.35 mmol/kg bw. The majority of subjects, (66.4%), received a dose of 0.05-0.1 mmol/kg bw. Overall, 54.5% of subjects were male. The ethnic distribution was 74.4% Caucasian, 11.9% Asian, 4.0% Black, and 9.6% of other ethnic groups. The average age was 53.7 years with an age range of 1.2 months to 97 years. For the 371 subjects who received other gadolinium drugs, subject's sex and the average age for adults was similar to Dotarem. There was a higher percentage of Caucasians and lower percentages of other races for the comparator drugs.**

The 2813 subjects who received Dotarem are the focus of this review. All subjects in the clinical trials who received either Dotarem or comparator drug were evaluated for adverse events. Adverse events were judged by the investigator as not related, doubtfully related, or possibly to study treatment and will be noted as reported for purposes of this review. This reviewer noted adverse event reporting was variable for each study with inconsistencies in reporting. For example, injection site tolerance, vital signs, and laboratory parameters, when evaluated, were assessed but changes may not have been considered to relate to the study drug and thus not considered as an adverse event. In the submission, the applicant noted that the methodology for adverse events evaluations was not described for studies conducted 20 or more years ago.

As noted in the above tables, in 3 phase 1 PK studies, a total of 50 subjects received Dotarem. The trials originated in the UK, (N = 6 subjects), and France, (N = 44 subjects, 8 of which were subjects with chronic renal failure). The applicant did not conduct any phase 1 PK studies using placebo and did not conduct any phase 1 or phase 2 dose ranging studies. The applicant noted 9 AEs for subjects that received Dotarem in these 3 phase 1 PK studies

Subjects in the phase 2 cardiac crossover study (for cardiac safety evaluation) did receive placebo injection as well as Dotarem. For this study, there were 6 “treatment emergent” AEs (mainly headache) noted in the Dotarem arm and 5 “treatment emergent” events in the placebo arm.

The population for the 49 clinical trials, the population for the CNS trials, and the population for the two pivotal CNS trials were similar in age and received similar doses of test product. The incidence of all AEs was slightly greater for the 2 pivotal trials but the incidence of related AEs was similar for all three groups. The types of AEs were similar for all groups.

For the all trials category, 62.4% of subjects were between 18 and 65 years of age. 66.4% of subjects received doses between 0.05-0.1mmol /kg bw. The applicant reported that 263 subjects treated with Dotarem, (9.3 %) experienced at least one AE and that 111 subjects, (3.9%) had AEs related to Dotarem. 130, (4.6%), had AEs not related to Dotarem. By system organ class, (SOC), the highest incidence of AEs in the in the clinical trials group were in general disorders and administration site conditions, (47 subjects, 1.7%), nervous system disorders, (31 subjects, 1.1%), gastrointestinal disorders, (27 subjects, 1.1%), skin and subcutaneous tissue disorders, (10 subjects, 0.3%), and investigations, (9 subjects, 0.3%). Nausea (0.6%), headache (0.5%), and injection site pain (0.4%) were the most common events by preferred term. 87.4% of AEs were mild or moderate. There were 8 deaths noted and 15 subjects including one pediatric subject age 5 years had non fatal serious adverse events (SAEs).

Of the 1632 subjects enrolled in CNS trials, 1329 received Dotarem and 276 received Magnevist. The dose and the age group studied were similar to the population for the 49 clinical trials, (64.6% received similar doses and 69.1% were in the same age range). 108 (8.1%) treated with Dotarem experienced at least one AE. There were 11 SAEs and a total of 10 AEs where the outcome was death, (7 deaths total). By system organ class, (SOC), the highest incidence of AEs in the CNS group were in general disorders and administration site conditions, (21 subjects, 1.6%), nervous system disorders, (14 subjects, 1.1%), gastrointestinal disorders, (13 subjects, 1.0%), skin and subcutaneous tissue disorders, (4 subjects, 0.3%), and investigations, psychiatric disorders, vascular disorders (2 subjects each, 0.2% each). Headache (0.8%), nausea (0.7%), and injection site pain (0.5%) were the most common AEs by preferred term.

For the two pivotal CNS trials, a greater percentage of subjects (391, 91.4%), received similar doses and 293, (68.5%), were between 18-65 years of age. For these two pivotal CNS trials, 57 subjects (13.3%) experienced AEs of which 4.4 % were considered by the applicant to be treatment related. By system organ class, (SOC), the highest incidence of AEs the pivotal studies group were in general disorders and administration site conditions, (7 subjects, 1.6%), gastrointestinal disorders, (6 subjects, 1.4%), nervous system disorders, (5 subjects, 1.2%), and investigations, (2 subjects, 0.5%). By preferred term, injection site pain and nausea were the most common AEs (0.9% each) followed by headache (0.5%). 84.1% of AEs were mild or moderate in intensity. There were 8 SAEs. 10 AEs were associated with 7 deaths.

141 pediatric subjects up to age 18 were studied, 7 between the ages of 1-24 months, 33 between 2 and 6 years, 58 between 6 and 12 years, and 43 between 12 and 18 years. 4 subjects (ages 12, 16, and 2 age 17 years), were enrolled in CNS trials other than the 3 pediatric trials and the -050 trial. 6 children (4.3%) reported AEs with headache as the most common AE experienced, (1.5%). The adverse event rate ranged from 4.7% in the 12-18 year old group to 14.3 % in the group age <2 years. Headache (1.5% incidence) was the most common AE with injection site pain and nausea were the other most common AEs. One pediatric subject experienced an SAE which the investigator did not consider related to Dotarem.

Only one subject withdrew from a clinical trial secondary to an adverse event, (pulmonary embolism leading to death, assessed by the investigator as not related to Dotarem).

371 subjects received a comparator gadolinium drug, most often Magnevist. 117 (31.5%) of these subjects were enrolled in the pivotal -050 CNS trial and 276 (70.4%) were enrolled in CNS studies. The overall adverse event rate for the comparator gadolinium agents was similar to Dotarem but treatment related events were assessed as greater, (3.9% for Dotarem versus 9.7% for other drugs). The number of subjects with at least one adverse event and the incidence of related events was also greater for the CNS studies, (8.1% with at least 1 AE and 3.7% related AEs for Dotarem versus 17.8% and 12.7% for other gadolinium drugs). For the 2 pivotal CNS trials, subjects with at least one AE and subjects with related AEs was slightly higher for Magnevist, (13.3% with at least 1 AE and 4.4% related AEs for Dotarem versus 17.1% and 7.7% for Magnevist). The types of events for Dotarem and the other gadolinium drugs were similar.

For all studies, the incidence of SAEs and deaths was greater for Dotarem than for the other agents, (0.8% versus 0.3 % SAEs and 8 deaths versus no deaths). There were 2 Dotarem related SAEs of moderate hypersensitivity and renal failure. For the CNS studies, the incidence of SAEs was also greater for Dotarem, (0.6% versus 0.4%). One pediatric subject experienced an SAE which the investigator did not consider related to

Dotarem. No pediatric subjects in the clinical trials received Magnevist or other gadolinium drug.

Table 22 summarizes the AEs and SAEs by body region and pediatric population reported in Dotarem clinical trials.

**Table 22: AEs and SAEs Reported in Dotarem Clinical Trials (N = 2813)**

Type of Study	Number of Patients Exposed to Dotarem	Patients With at Least one Adverse Event (AE)	Number of Serious Adverse Events (SAE)
PK	90	19 (21.1%)	0 (0.0%)
CNS (Adults)	1188	107 (9.0%)	9 (31.0%)
Whole Body	502	44 (8.8%)	9 (31.0%)
MRA	892	92 (10.3%)	9 (31.1%)
CNS (Pediatric)	141	1 (0.7%)	2 (6.9%)
<b>Total</b>	<b>2813</b>	<b>263 (9.3%)</b>	<b>29</b>

AE, SAE, death, and discontinuation data was further summarized for the adult and pediatric populations in response to an Information Request dated 1-18-13. This response is reproduced in Tables 23 and 24 below.

**Table 23: Dotarem Clinical Trials; Summary of AEs, SAEs, Deaths, Discontinuations\*\* (1-18-13 Response to FDA Information Request)**

Category	All AEs		Related AEs*	
No. of AEs	363		149	
No. (%) of Subjects with at least 1 AE	263 (9.3%)		111 (3.9%)	
Mild	182 (subjects)	258 (AEs)	85 (subjects)	116 (AEs)
Moderate	45 (subjects)	59 (AEs)	20 (subjects)	27 (AEs)
Severe	25 (subjects)	32 (AEs)	5 (subjects)	5 (AEs)
Unknown	11 (subjects)	14 (AEs)	1 (subject)	1 (AEs)
Not reported/not collected	6 (subjects)		0	
No. (%) of subjects with at least 1 SAE	23 (0.8%)		2 (0.07%)	
No. (%) of deaths	8 (0.3%)		0	
No (%) of subjects discontinued due to an AE	1 (0.04%)		0	

\* Among 363 AEs, drug relationship for 21 AEs are not reported or not collected

\*\* N = 2813

**Table 24: Dotarem Clinical Trials Summary of AEs by Subject Age in The Pediatric Population\* (1-18-13 Response to FDA Information Request)**

Category	All AEs		Related AEs	
No. of AEs	15		10	
No. (%) of Subjects with at least 1 AE	10/38 (26.3%)		6/38 (15.8%)	
2-6 years	2 (patients)	3 (AEs)	1 (patient)	1 (AE)
6-12 years	6 (patients)	8 (AEs)	4 (patients)	6 (AEs)
12-18	2 (patients)	4 (AEs)	1 (patient)	3 (AEs)

\*N = 38

As noted in these three tables, the overall incidence was greater for the PK studies and less for the pediatric population. SAE incidence was similar for body region in the adult population, less for the pediatric population. The rate and severity of AEs was comparable for the pooled analyses and did not identify a specific safety concern. Overall, the incidence and type of drug related AEs was similar to other gadolinium agents.

The applicant used baseline demographics for various relevant medical conditions and conducted subgroup analyses for AEs by various medical conditions based on subject history. Safety using AE rate was evaluated based on subject enrollment characteristics of renal disease, hepatic disease, cardiac disease, diabetes, allergic history, and history of allergy to contrast agents. Comparing enrollment for the all subjects, CNS studies, and pivotal trials categories, apart for the subgroup contrast allergy, the percent of subjects with a positive disease history was less for the CNS and pivotal trials which is expected based on concomitant factors such as medical conditions in patients with vascular disease who would be referred for an MRA study. Enrollment of subjects with a history of contrast allergy was 1.8%, 1.6%, and 1.9% for these groups respectively. Subjects enrolled in the clinical trials that received comparator drugs had underlying medical conditions similar to the all subjects category. Percentage of AEs for both Dotarem and comparators was similar in subjects with renal disease, hepatic disease, and a history of allergies and was decreased for subjects with cardiovascular disease and diabetes. Of 50 subjects that reported a history of contrast allergy, 11 AEs were reported and 8 (2.2%) of these were considered related to Dotarem. 5 AEs occurred for the 0.09-0.11 mmol/kg bw dose and 3 occurred for the 0.2-0.3 mmol/kg bw dose. When drug demographic interactions were assessed, the applicant noted no specific gender, age, or race related trends.

Table 25 lists all drug related AEs  $\geq 0.2\%$  incidence in Dotarem treated subjects, also listing below the table reactions occurring less than 0.2% incidence, most of which were noted at an 0.1% incidence.

**Table 25: Related Adverse Events in  $\geq 0.2\%$  of Subjects in All Studies\***

<b>System Organ Class Preferred Term</b>	<b>Rate (%) n=2813</b>
Nausea	0.6%
Headache	0.5%
Injection Site Pain	0.4%
Injection Site Coldness	0.2%
Burning Sensation	0.2%

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

Summary results of the various safety parameters that were assessed were as follows:

- Vital signs (vital signs, blood pressure, and ECG): No relevant or consistent changes in blood pressure or heart rate were noted with minimum fluctuation changes attributed to underlying conditions or to procedure related stress. Most changes did not lead to AE reporting.
- A thorough ECG study which evaluated the effect of Dotarem on cardiac repolarization demonstrated no effect of gadobutrol on cardiac repolarization for doses up to 0.3 mmol/kg bw, there were no subjects with a corrected QT interval (by Fredericia method, QTcF) greater than 480 msec or an increase from baseline of greater than 60 msec, and no abnormalities were detected in the ECGs. The cardio-renal QT team was consulted with summary findings noting that Dotarem has no effect on cardiac repolarization.
- Most clinical monitoring and laboratory parameters revealed no relevant changes from baseline or any clinically significant laboratory abnormalities. Some of the changes noted were considered chronically typical, some were statistically significant but of no biological significance, and some were explained by study conditions, for example a post prandial state.

*Reviewer's Comments:*

1. Summary AE data is comparable to other approved GBCAs.

2. *There were no PK studies conducted in the pediatric population to assess dose and safety in this population.*

3. *No dose ranging studies were conducted however, regarding safety as monitored by AE rate, the incidence of AEs was similar for the proposed 0.1 mmol/kg bw dose and the 0.2-0.3 mmol/kg dose.*

4. *Based on US FDA approved GBCAs, overall safety monitoring was limited. No trending or safety signals were noted in the limited population that was studied.*

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For evaluation of safety, this reviewer included all the information from the 49 clinical trials (50 subjects treated with Dotarem in phase 1 trials, 390 subjects treated with Dotarem in phase 2 trials, 2079 subjects treated with Dotarem in phase 3 trials, and 294 subjects treated with Dotarem in phase 4 trials). 2813 subjects in all clinical trials received Dotarem. 371 subjects in clinical trials received Magnevist and other gadolinium agent as comparator drugs. The total number of subjects in clinical trials including subjects who were administered a comparator drug was 3043 adults and 141 children. The applicant submitted pediatric data for children up to age 18. This reviewer noted that 7/99 subjects in the 3 supportive pediatric trials, 2/38 subjects in - 050 trial, and 2/4 subjects enrolled in other CNS trials were listed by the applicant as age 16-17 years, (2 others were age 16 and 12 years) for a total of 130 pediatric subjects. The total number of clinical trial studies conducted by Guerbet using Dotarem including additional whole body studies (9) and MRA studies (13) was 49 and includes 6 phase 4 studies, 27 phase 3 studies, 12 phase 2 studies, and 4 PK studies with 1 of the PK studies considered to be a phase 2 study. By body region, there were 3 PK studies, 1 cardiac study, 23 CNS studies, and 22 studies of other body regions. Safety evaluation included evaluation of 5 post marketing studies (a 6<sup>th</sup> study is ongoing) and global pharmacovigilance reports.

One of the phase 2 special safety studies was a thorough QT/QT<sub>c</sub> study. The applicant conducted two additional special safety studies, a phase 3 study in subjects with various renal diseases comparing efficacy and safety of Dotarem to Magnevist and a phase 4 study to evaluate subjects with stable renal insufficiency.

The 2 major clinical studies supporting the efficacy and safety of Dotarem in the US are pivotal phase 3 studies, (study DGD-44-050 and DGD-44-051). 3 pediatric clinical trials, DGD-3-15, DGD-3-16, and DGD-3-29 are considered as supportive of the proposed pediatric indication.

The patient populations that participated in the above noted phase 3 pivotal studies consisted of subjects referred for contrast-enhanced MRI of the CNS either based on results from a previous imaging procedure, with subject enrollment in the -051 study also based on additional referral for a biopsy or surgical procedure. Referral for the 3 pediatric supportive studies was for diagnosis, staging, and evaluation for recurrence of CNS tumors (DGD-3-15 and DGD-3-16) or for diagnostic efficacy, contribution to diagnosis, and effect on therapeutic approach (study DGD-3-29).

As already noted, including the pivotal phase 3 studies, the majority of phase 2-4 studies, (23), were performed for a CNS indication. 9 body studies (to include the two special safety studies), 13 MRA studies, 3 PK studies and an additional special safety cardiac study were also conducted. Approximately 66.4% of subjects received a 0.05-0.1 mmol/kg bw dose.

The safety data was also evaluated according to subject pooling, (all studies, CNS studies, and 2 pivotal trials), see section 7.1.3 below. Demographic data from the pools was evaluated for sex, age, weight, height, race, and various ongoing pathologies such as allergic history and renal disease. Table 27 in section 7.2.1 is a listing of the studies by location, phase and type, study design, Dotarem dose, safety parameters (monitors) with summary of safety results, and subject ages/other limited demographics.

The majority of subjects received only one dose (exposure) of the drug.

#### 7.1.2 Categorization of Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) Version was used for categorization (coding) of adverse events.

#### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Analysis of safety data included the following: integrated analysis pools for all 49 clinical trials, for the 23 CNS clinical trials, and for the 2 pivotal CNS trials. Analysis of pediatric subjects in the -050 CNS clinical trial was done as a limited additional analysis.

Pooling of data for purposes of analysis was done as requested by the FDA. Data used to create the safety pools is contained in Table 26 below

**Table 26: Integrated Analysis Pools**

<b>Integrated Analysis Pools</b>	<b>Study Phase</b>	<b>Number of Studies</b>	<b>Subjects Enrolled and Treated</b>	<b>Dotarem Subject Treatments*</b>
<b>All Studies</b>	<b>All Dotarem or Dotarem/Comparator studies</b>	49	3184	2813
	<b>Comparator Studies</b>	5	917	546
	<b>All PK and special population studies</b>	6	180	180
	<b>Total</b>	<b>49</b>	<b>3184</b>	<b>2813</b>
<b>All CNS Studies Phase 2 to Phase 4</b>	<b>Dotarem/Comparator Phase 2</b>	11	341	331
	<b>Phase 3</b>	10	1165	889
	<b>Phase 4</b>	2	109	109
	<b>Total</b>	<b>23</b>	<b>1605</b>	<b>1329</b>
<b>CNS Pivotal Studies</b>	<b>Dotarem/Comparator Phase 3</b>	2	395	278

\* Subjects from crossover study DGD-44-052 who received Dotarem were counted in the Dotarem group

The integrated safety analysis was performed for each data pool to include comparator studies in each pool.

All variables were analyzed by descriptive statistical methods. Data were presented by mean, standard deviation, minimum, median, and maximum. Frequency tables were generated for categorical data.

## 7.2 Adequacy of Safety Assessments

All subjects who received the study drug were included in the safety evaluations. 66.4% received doses between 0.05-0.1 mmol/kg at varying flow rates. Approximately 82.3% of subjects received a dose between 0.09-0.11 mmol/kg bw, 4.9% received a dose of 0.18-0.22 mmol/kg bw, and 5.9% received a dose between 0.27-0.33 mmol/kg bw. 371 subjects received a comparator gadolinium drug, also at a dose of 0.1 mmol/kg bw.

All subjects in clinical trials were assessed for AEs. The AE monitoring period varied from shortly after Dotarem injection (approximately 15 minutes) to 24 hours after injection, with occasional monitoring at 48 or 72 hours. AEs were assessed either by spontaneous complaints from subjects or by directed questions. Most studies did not assess the category of “any AEs.” Evaluation of adverse events included mainly treatment emergent events defined as those that occurred during treatment or within 30 days after the last dose of study drug, events that were present at baseline but that increased in severity during the study, or events that were considered treatment related despite no increase in severity from baseline. The applicant noted that the methodology for adverse events evaluations was not described for studies conducted 20 or more years ago. This reviewer noted on review of clinical trial study reports that when laboratory or vital sign or injection site changes occurred, reporting the changes was variable. These changes may or may not have been considered as AEs and many of the changes were reported as “clinically significant but chronically typical.” Some events currently considered as AEs may not have been considered as AEs at the time of the study report. For example, the phase 2/3 study 3-34 noted subject reactions of paresthesia, convulsions, and headache right after injection but did not list these reactions as AEs. In addition, 45% of subjects in clinical trials were assessed by a visual analogue scale, (VAS). This scale was used to record the subjective global discomfort feeling in subjects immediately after Dotarem injection and may have included injection site pain.

Vital signs, when assessed, were generally more frequently assessed early after injection during the course of the study in tandem with more frequent AE assessments. As already noted, vital sign shifts may or may not have been assessed as adverse events. Changes in systolic and diastolic blood pressure were sometimes considered as biphasic changes secondary to the stress of the study despite the fact that the changes may have persisted for up to 24 hours. The applicant noted that Guerbet provided pre-defined value ranges for vitals signs for some studies but that assessment was the responsibility of the investigator.

ECG monitoring was performed as part of the PK studies and for 100 adults enrolled in the -050 study and was satisfactory.

Laboratory evaluations included hematologic and/or biochemistry parameters. Laboratory evaluations, when performed, were comprehensive with most evaluations at baseline and 24 hours. The greatest number of subjects with laboratory evaluations was enrolled in the 5 US IND studies (one CNS study and 4 MRA studies). As was the case for vital signs, Guerbet considered assessment of laboratory parameters to be the responsibility of the investigator. Individual normal site specific values were included with each study. As has already been

**noted, many laboratory assessments were considered “clinically significant but chronically typical.”**

Table 27 below lists each clinical trial and the safety parameters assessed. The table does not include the additional subjective monitor, the visual analogic scale (VAS) that the applicant used in 25 of the 49 clinical trials. As noted in the table, there was a range of safety monitoring for the studies with a wide range of dose administration rates also noted. Drug administration dose, injection method, and flow rate will be addressed in section 7.3.5.

**Table 27: Clinical Trial Safety Evaluations**

<b>Study Number</b>	<b>Indication Study Phase</b>	<b>Number of Subjects</b>	<b>Dotarem Dose And Administration*</b>	<b>Clinical Safety Monitoring</b>
3-6	PK Phase 1 Healthy volunteers	6	0.1 mmol/kg 8 mL/min	Lab, Vital Signs, ECG, AEs
3-28	PK Phase 1 Renal failure	12 (4 healthy volunteers)	0.1 mmol/kg Single rapid injection	Lab, Vital Signs, ECG, AEs
3-48	PK Phase 1 Healthy Volunteers	32	0.1-0.3 mmol/kg 2 mL/min	Lab, Vital Signs, ECG, AEs
44-039	Special Safety Phase 2 Cardiac Disorders	40	0.1-0.3 mmol/kg 1-2 mL/sec	Lab, Vital Signs, ECG, AEs
3-7	CNS Phase 2	56	0.1 mmol/kg 7.5 mL/min	AEs

3-11	CNS Phase 2	19	0.1 mol/kg 7.8 mL/min	Lab, EEG, AEs
3-4	CNS Phase 2	20	0.1 mmol/kg 7.1 mL/min	Lab, AEs
3-8	CNS Phase 3	54	0.1 mmol/kg 4.5 mL/min	AEs
3-1	CNS Phase 2	10	0.1 mmol/kg 4.9 mL/min	Lab, AEs
3-12	CNS Phase 2	50	0.1 mmol/kg 3 mL/min	AEs
3-14	CNS Phase 3	55	0.1 mmol/kg 2.9 mL/min	AEs
3-23	CNS Phase 3	50	0.1 mmol/kg give over 1 min	AEs
3-5	CNS Phase 2	10	0.1 mmol/kg 2-3 mL/min	Lab, AEs
3-9	CNS Phase 2	22	0.1 mmol/kg 3.7 mL/min	Lab, AEs
3-16	CNS Phase 2	20	0.1 mmo/kg 2.4 mL/min	AEs

<b>3-15</b>	<b>CNS Phase 2</b>	<b>29</b>	<b>0.1 mmol/kg 3 mL/min may or may not dilute in saline</b>	<b>Lab (20), AEs</b>
<b>3-17</b>	<b>CNS Phase 2</b>	<b>10</b>	<b>0.1 mmol/kg 4.5 mL/min</b>	<b>Lab, AEs</b>
<b>3-3</b>	<b>CNS Phase 2</b>	<b>30</b>	<b>0.1 mmol/kg 4.1 mL/min</b>	<b>Lab, AEs</b>
<b>3-21</b>	<b>CNS Phase 3</b>	<b>50</b>	<b>0.1 mmol/kg 2.7-6.7 mL/min</b>	<b>AEs</b>
<b>3-20</b>	<b>CNS Phase 3</b>	<b>48</b>	<b>0.1 mmol/kg Bolus</b>	<b>AEs</b>
<b>3-31</b>	<b>CNS Phase 3</b>	<b>149</b>	<b>0.1 mmol/kg Fast bolus</b>	<b>AEs</b>
<b>3-29</b>	<b>CNS Phase 4</b>	<b>50</b>	<b>0.1 mmol/kg Rapid bolus</b>	<b>AEs</b>
<b>3-34</b>	<b>CNS Phase 2</b>	<b>45</b>	<b>0.3 mmol/kg Rapid injection</b>	<b>Lab, AEs</b>
<b>3-33</b>	<b>CNS Phase 3</b>	<b>65</b>	<b>0.3 mmol/kg Not given</b>	<b>AEs</b>
<b>3-40</b>	<b>CNS Phase 4</b>	<b>59</b>	<b>0.2 mmol/kg 5-13 mL/sec then 20 mL rinse with normal saline</b>	<b>AEs</b>

<b>3-44</b>	<b>CNS Phase 3</b>	<b>150</b>	<b>0.1 mmol/kg 1-2 mL/sec</b>	<b>Vitals, AEs</b>
<b>44-050</b>	<b>CNS Phase 3</b>	<b>278</b>	<b>0.1 mmol/kg 2 mL/sec—adult 1.1 mL/sec—ped</b>	<b>Lab, Vitals, ECG (100), AEs</b>
<b>3-22</b>	<b>Body Phase 3</b>	<b>24</b>	<b>0.1 mmol/kg 8-16 mL/min</b>	<b>AEs</b>
<b>3-13</b>	<b>Body Phase 3</b>	<b>30</b>	<b>0.1-0.2 mmol/kg Over 1 minute</b>	<b>AEs</b>
<b>3-19</b>	<b>Body Phase 3</b>	<b>39</b>	<b>0.1-0.2 mmol/kg 3-12 mL/min as rapid IV over 15 sec to 1 min</b>	<b>AEs</b>
<b>3-2</b>	<b>Body Phase 2</b>	<b>20</b>	<b>0.1 mmol/kg 3.3 mL/min</b>	<b>Lab, AEs</b>
<b>3-26</b>	<b>Body Phase 4</b>	<b>10</b>	<b>0.2 mmol/kg 2 mL/sec bolus</b>	<b>Lab, AEs</b>
<b>3-32</b>	<b>Body Phase 3</b>	<b>80</b>	<b>0.1 mmol/kg Bolus &lt;10 sec</b>	<b>AEs</b>
<b>3-49</b>	<b>Body Phase 3</b>	<b>120</b>	<b>0.1 mmol/kg 1.5-3 mL/sec, mean 2.1 mL/sec</b>	<b>Vitals, AEs</b>
<b>3-50</b>	<b>Body</b>	<b>109</b>	<b>0.1 mmol/kg</b>	<b>Vitals, AEs</b>

	<b>Phase 3</b>		<b>1-2 mL/sec followed by 10 mL saline infusion</b>	
<b>44-044</b>	<b>Body Phase 4</b>	<b>70</b>	<b>0.1 mmol/kg rate “according to usual practices” 1.4-2.6 mL/sec</b>	<b>Lab, Vitals, AEs</b>
<b>3-36</b>	<b>MRA Phase 3</b>	<b>41</b>	<b>0.1 mmol/kg 2 mL/sec followed by 20 mL saline at 2 mL/sec</b>	<b>AEs</b>
<b>3-38</b>	<b>MRA Phase 3</b>	<b>40</b>	<b>0.1 mmol/kg 2 mL/sec followed by 20 mL saline at 3 mL/sec</b>	<b>Vitals, AEs</b>
<b>3-39</b>	<b>MRA Phase 3</b>	<b>40</b>	<b>0.1 or 0.2 mmol/kg 2 mL/min followed by 20 mL normal saline “chaser”</b>	<b>AEs</b>
<b>3-37</b>	<b>MRA Phase 3</b>	<b>35</b>	<b>0.1-0.2 mmol/kg 1-2 mL/sec followed by 20 mL normal saline flush at 2 mL/sec</b>	<b>AEs</b>
<b>3-42</b>	<b>MRA Phase 4</b>	<b>6</b>	<b>0.125-0.25 mmol/kg 2 mL/sec followed by 20 mL saline infusion at 2 mL/sec</b>	<b>Vitals, AEs</b>
<b>44-38</b>	<b>MRA Phase 3</b>	<b>100</b>	<b>0.1 mmol/kg 1-2 mL/sec</b>	<b>Vitals, AEs</b>

44-42	MRA Phase 4	92	0.1 mmol/kg 1-2 mL/sec	Vitals, AEs
44-046	MRA Phase 3	32	0.1 mmol/kg 2 mL/sec	Lab, Vitals, AEs
44-047	MRA Phase 3	10	0.1 mmol/kg 1-3 mL/sec	Lab, Vitals, AEs
44-048	MRA Phase 3	200	0.1 mmol/kg 2 mL/sec	Lab, Vitals, AEs
44-049	MRA Phase 3	187	0.1 mmol/kg 2 mL/sec	Lab, Vitals, AEs
44-052	MRA Phase 4	17	0.1 mmol/kg 1 mL/sec followed by 25-30 mL saline flush	Vitals, AEs
44-045	MRA Phase 3	92	0.1 mmol/kg 1 mL/sec	Vitals, AEs

\* Flow rates according to study reports. When a range was reported with tables of individual or group results; the mean was used if there were small deviations.

Table 28 below provides a percentage breakdown of safety parameters in Dotarem clinical development studies based on indication/body region/study type. Apart from the PK and cardiac special population study, the most comprehensive safety monitoring was seen in the MRA studies, 4 of which were conducted under US IND and SPA process. For the CNS indication, only the -050 pivotal study which was conducted under US IND SPA process monitored both laboratory parameters and vital signs. An additional 186 subjects in multiple studies were monitored for laboratory parameters only and 150 subjects in the DGD-3-44 (-051 re-read study) were monitored for vital signs only.

**Table 28: Dotarem Clinical Trials Safety Monitoring Summary**

<b>Study Type</b>	<b>Total Number of Subjects</b>	<b>Lab and Vital Sign Monitor N (%)</b>	<b>Lab and Vital Signs + Lab + Vital Signs N (%)</b>
<b>PK &amp; Cardiac</b>	<b>90</b>	<b>90 (100%)</b>	<b>90 (100%)</b>
<b>CNS</b>	<b>1329</b>	<b>278 (20%)</b>	<b>Lab-186 Vital signs-150 Total-514 (38%)</b>
<b>Body</b>	<b>502</b>	<b>70 (14%)</b>	<b>Lab-30 Vital signs-229 Total-329 (65%)</b>
<b>MRA</b>	<b>892</b>	<b>429 (47%)</b>	<b>Vital signs-301 Total-730 (81%)</b>
<b>Total (Labs)</b>	<b>216</b>		<b>1083 (38%)</b>
<b>Total (Vital Signs)</b>	<b>680</b>		<b>1547 (55%)</b>
<b>Total (Labs and/or Vital signs)</b>	<b>2813</b>	<b>867 (31%)</b>	<b>1663 (59%)</b>

**As can be seen in the above table, only a total of 31% of clinical trial subjects received comprehensive safety monitoring. This percent only increased to 59%**

**when subgroups analyzed by vital signs only or laboratory parameters only were added.**

**After assessment of the safety monitoring and safety data provided by the applicant, this reviewer concluded that this drug development lacked appropriate safety monitoring. However, although safety monitoring for the clinical trials overall was generally insufficient it was adequate for the -050 CNS study and 4 MRA studies that were conducted under US IND.**

Regarding the pediatric indication, as noted on the above tables, this reviewer's opinion is that there is insufficient safety data to support the CNS indication for children under age 2 years based on limited safety monitoring and the number of subjects studied. Additionally, as has already been noted, PK studies to confirm the distribution and elimination of Dotarem in children were not conducted. Using the above tables to summarize pediatric safety monitoring, it is noted that the 99, (92 ages 1.2 months to 17) subjects in the 3 pediatric trials (DGD-3-15, DGD-3-16, and DGD-3-29) were all assessed for adverse events however only 20 subjects in the DGD-3-15 trial received safety monitoring by laboratory evaluations. Out of the total number of children in these 3 clinical trials, only 7 subjects were under age 2 years and only 2 were in the group that received laboratory evaluations. The 36 pediatric subjects, ages 2-18 years, who were enrolled in the -050 study were monitored for safety with laboratory parameters and vital signs similar to the adult population. Although this group also included 2 subjects age 17, this reviewer noted that the age groups studied were diverse and the monitors were comprehensive so that overall safety is sufficient for approval in the 2-17 year age group.

Based on the information provided in Table 27, this reviewer has additional concerns regarding the administration of Dotarem to children. As noted for the three pediatric studies and for the -050 study, Dotarem administration rate and methods was variable for the studies. The mean flow rate for Study DGD-3-15 was 2.4 mL/min and Dotarem may have been diluted in saline. The mean administration rate for the DGD-3-16 study was 3 mL/min. For the DGD-3-29 phase 4 study, Dotarem was administered as a bolus, no rate given. The rate of Dotarem administration for children in the -050 study was 1-2 mL/sec.

In general, this reviewer concluded that the majority of safety assessments conducted and analyzed were incomplete for all age groups. This is a particular concern for the pediatric population given the lack of any pediatric PK studies. In particular, this reviewer does not consider safety monitoring was appropriate for this diagnostic agent for the pediatric indication for children under age 2. Although there were limitations to safety monitoring, for most studies, subject compliance was satisfactory and the information provided did not suggest any trending regarding missing or non diagnostic values.

*Reviewer's Comments:*

1. *This reviewer considers that there was inadequate safety monitoring for the clinical trials based on relative paucity of comprehensive data and variability in reporting.*

2. *This reviewer considers that there is insufficient data to support approval in children under age 2. No PK studies were conducted in children and there were no dose ranging studies. Only 7 subjects under age 2 were enrolled in clinical trials and only 2 of these subjects received a comprehensive laboratory assessment.*

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

2672 subjects exposed were adults >18 years of age most of whom received a single administration of study drug. 371 adult subjects who participated in the comparator studies were exposed to an alternate gadolinium drug with a few subjects exposed to both drugs as part of crossover studies. 141 pediatric subjects (up to age 18) were exposed to study drug. 66.4% of subjects received a 0.05-0.1 mmol/kg dose of study drug although not necessarily for the proposed indication.

By actual dose range for 2807 subjects, the mean dose was 0.12 mmol/kg bw with a minimum/maximum dose of 0.01/0.35 mmol/kg bw. Using a deviation of 10% from theoretical dose injected, 2323 received a dose of 0.09-0.11 mmol/kg bw, 138 subjects received a dose of 0.18-0.22 mmol/kg bw, and 166 subjects received a dose of 0.27-0.33 mmol/kg bw.

Regarding exposure to study drug, 1457, (51.8%), subjects were listed as “unknown” with respect to the number of injections. 1139, (39.8%) received a single injection and 237, (8.4%), received 2 injections. For subjects where the number of injections was known, the mean dose for a single injection was 0.1 mmol/kg bw and was 0.25 mmol/kg bw for two injections. Study drug was administered intravenously either manually or by an injector at variable rates. In a few instances, Dotarem was diluted in saline. Dotarem injection was followed by a saline flush in several studies.

The applicant analyzed mean demographics. A breakdown by gender showed dose administration ranged per dose group from 40-60% of subjects apart from the 0.05-0.09 mmol/kg bw group where 76.0% of subjects injected were males and 24.0% were females. The mean age of subjects injected by dose group was approximately 50 years for all groups. By racial group, 72.4% of Caucasians, 4.5% of Blacks, 12.6% of Asians, and 10.6% of “Other races” received an 0.09-0.11 mmol/kg dose. 2.1% of Blacks received a 0.20-0.30 mmol/kg bw dose. 6.3% of Asians received this dose also with 9.0% of Asians receiving a 0.11-0.20 mmol/kg bw dose and 1 Asian receiving a dose

less than 0.05 mmol/kg bw. 5.0% of subjects in the Other category received a dose ranging from 0.11-0.20 mmol/kg bw and 2.1% received a dose ranging from 0.2-0.3 mmol/kg bw. The racial demographics and doses are reflective of the study regions with a high proportion of Caucasians in the earlier clinical studies in which the higher doses were studied.

Table 29 presents a summary of all clinical trial studies. For completeness, this table includes the safety parameters that were assessed and a brief summary of the safety results presented in study reports. The table includes the clinical trial study phase and design, study drug dosage and administration rate, safety parameters and major safety summary by study, demographics for region, sex, and age, and study indication/type. The demographics of race are presented only for the 5 US IND studies and for isolated other studies. As has already been noted, the overall study population was mostly Caucasian which is compatible with the study regions, (mostly in the EU). 2813 subjects enrolled in clinical trials received Dotarem. 371 received a comparator drug. From this table, one can see that by study phase, approximately 2% of subjects were enrolled in phase 1 PK studies, 13% in phase 2 studies, 70% in phase 3 studies, and 14 % in phase 4 studies. These numbers are appropriate for clinical development.

**Table 29: Overview of All Clinical Studies for Dotarem Safety and Major Safety Summary**

<b>Study # Study year Study sites location(s )</b>	<b>Subject Age Range (yrs), # Subjects # Exposed (Study Drug) Other Demograph.</b>	<b>Study Phase and Design</b>	<b>Study Drug Dosage and Admin Rate</b>	<b>Safety Parameters and Major Safety Summary * VAS-45% of studies, not included</b>	<b>Indication/Type of Study/Study Objectives</b>
DGD-3-6; 1987; UK	21-29; 6; 6	1 NR, O, S	0.1 mmol/kg 8 mL/min	Safety: Lab, vital signs, AEs  Summary: PK is a 2 compartment model with rapid distribution and urinary elimination; Numerous deviations from normal values but none significant notably variations in iron excretion but	PK; Study of the excretion of Dotarem in the blood, urine, and feces of healthy male volunteers

				remaining within normal limits and high zinc urinary excretion attributed to young age; no change in vital signs; AEs(1)	
DGD-3-28; 1990; France	20-59; 12; 12	1 NR, O, S	0.1 mmol/kg Single rapid injection	Safety: PK parameters, lab, vital signs, AEs Summary: Decreased clearance with increased renal failure, 24 hours excretion 93% for normals, 75% for moderate failure, 49% for severe failure with half life of 1.6 hrs, 5 hrs, 14 hrs; no clinically significant lab abnormalities; no change in vital signs; AEs (4)	PK: in 4 healthy volunteers and 8 subjects with renal impairment; Study of the pharmacokinetics of Dotarem in patients with chronic renal failure
DGD-3-48; 2004; France	18-45; 32; 32	1 NR, O, S	0.1mmol/kg + 0.2 mmol/kg, total 0.3 mmol/kg 2mL/min	Safety: Lab, vital signs, ECGs, AEs Summary: PK parameters following single injection and triple dose (2 injections) showed drug distribution differences between males and females based on body weight, dose proportionality and confirmed, rapid clearance from plasma by renal clearance; safety for lab, vital signs, ECGs	PK study of Dotarem after injection of 0.1 mmol/kg dose and 0.1 + 0.2 mmol/kg dose in healthy male and female volunteers

				showed no trending or relevant changes from baseline, AEs (4)	
DGD-44-39; 2004; France	19-75; 40; 40	2 DB, R	0.3 mmol/kg 1-2 mL/sec	Safety: Lab, vital signs, ECGs, AEs  Summary: QT study using Dotarem and placebo, no effect on QT or QTc interval or other ECG parameters, isolated and non significant lab and vital sign changes, AEs (6 Dotarem, 5 placebo)	Special safety QT crossover study with 12-lead ECGs
DGD-3-17; 1988; France	18-77; 20; 10	2 R, DB, C, S	0.1 mmol/kg 4.5 mL/min	Safety: Lab, AEs  Summary: 82% modified diagnosis compared to 40% for Magnevist with therapeutic management changed for 4/9 with Dotarem and 4/4 with Magnevist; lab tests significantly varied for both groups, (Ca, alk phos, Cu for Dotarem) but no significance, AEs (0)	CNS randomized double blind comparative parallel group study comparing efficacy and safety of Dotarem to Magnevist
DGD-3-31; 1988; France, Belgium, Switzerland	18-79; 299; 149 Dotarem	3/4 R, DB, C, M	0.1 mmol/kg Fast bolus	Safety: AEs  Summary: CNS diagnostic usefulness confidence and assistance in management similar for both drugs; 71 % of AEs seen between 1-6 hours, (AEs 26 Dotarem, 29	CNS randomized double blind comparative parallel group study comparing efficacy and safety of Dotarem to Magnevist

				Magnevist); 71% of effects seen in 1-6 hours	
DGD-3-07; 1987 France	18-82; 56; 56	2 NR, O, S	0.1 mmol/kg 7.5 mL/min	Safety: AEs  Summary: CNS (53) and bone/soft tissue (3) with modification of diagnosis in 51%, change in management in 45%; AEs (2 hypersensitivity)	Neurological CNS (53) and bone and soft tissues (3) magnetic resonance imaging, general safety and diagnostic efficacy
DGD-3-11; 1987; France	24-76; 19; 19	2 NR, O, S	0.1 mmol/kg 7.8 mL/sec	Safety: Coagulation factors, EEG, AEs  Summary: Modification or specification of diagnosis in 68% and management change in 47%; no change in EEG or clotting parameters, AEs (0)	CNS MRI for neurological investigation for cerebral safety, effects on clotting, and diagnostic efficacy in neurological investigations
DGD-3-04; 1987; France	17-72; 20; 20	2 NR, O, S	0.1 mmol/kg 7.1 mL/min	Safety: Lab, AEs  Summary: 75% modification in diagnosis and 85% modification of therapeutic approach; minor variations in hematologic parameters remaining within normal range except for sodium and CO2 which were elevated pre study also and for 2 urinary parameters of creatinine clearance and BUN;	CNS renal and hepatic safety and diagnostic efficacy in neurological investigations

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				AEs (0)	
DGD-3-08; 1987; France	20-72; 54; 54	3 NR, O, S	0.1 mmol/kg 4.5 mL/min	Safety: AEs  Summary: Change in therapeutic management in 96%; AEs (0)	CNS MRI for general safety and diagnostic efficacy
DGD-3-01; 1987; France	21-66; 10; 10	2 NR, O, S	0.1 mmol/kg 4.9 mL/min	Safety: Lab, AEs  Summary: Change in diagnosis in 70% and change in management in 60%; safety for urinary lab parameters are extrapolated values with some creatinine values increasing and decreasing but no trending and no significant variation otherwise in labs apart from blood glucose at 2 hours attributed to post prandial state; AEs(0)	CNS MRI for renal safety and diagnostic efficacy in neurological investigations
DGD-3-12; 1987; France	18-76; 50; 50	2 NR, O, S	0.1 mmol/kg 3.0 mL/min	Safety: AEs  Summary: Change in diagnosis in 67% and modification of therapeutic management in 61%; AEs (5 AEs in 3 subjects with 3 hypersensitivity AEs in one subject)	CNS MRI for general safety and diagnostic efficacy in neurological investigations
DGD-3-14; 1987; France	18-70; 55; 55	3 NR, O, S	0.1 mmol/kg 2.9 mL/min	Safety: AEs  Summary: Modification of diagnosis in 69% and revision of therapeutic	CNS general safety and diagnostic efficacy of Dotarem in cerebrospinal MRI

				management in 73%; AEs (8 categories of AEs noted in 7 subjects with 4 subjects experiencing 4 similar AEs, AEs were neurological and delayed)	
DGD-3-23; 1988 France	18-69; 50; 50	3 NR, O, S	0.1 mmol/kg Give IV over 1 minute	Safety: AEs  Summary: Change in diagnosis in 15% of cases with change in therapeutic approach in 29%; AEs (1)	CNS neurological magnetic resonance imaging, general safety and diagnostic efficacy
DGD-3-5; 1987; Belgium	18-74; 10; 10	2 NR, O, S	0.1 mmol/kg 2 mL/min (planned 3)	Safety: Lab, AEs  Summary: Modification of diagnosis in 50% and modification of therapeutic management in 30%; lab urine and blood parameters with significant changes in calcium and platelets but no biological significance; AEs (0)	CNS neurological investigation by magnetic resonance imaging, laboratory safety and diagnostic efficacy
DGD-3-9; 1988; Belgium	25-75; 22; 22	2 NR, O, S	0.1 mmol/kg 3.7 mL/min	Safety: Lab, AEs  Summary: Change in diagnosis in 45% and change in therapeutic management in 36%; safety for hepatic and renal parameters with laboratory changes such as change in BUN and blood proteins significant and non significant	CNS with Dotarem renal and hepatic safety and general safety and diagnostic efficacy in neurological investigations

				changes of increased potassium, but with these values clinically insignificant ; AEs (1)	
DGD-3-3; 1988; France	21-75; 30; 30	2 NR, O, S	0.1 mmol/kg 4.1 mL/min	Safety: Lab, AEs  Summary: CNS safety assessed by 15 hematological parameters showed statistically significant variations for 7 subjects, 5 decreases and 2 increases, of no biological significance, AEs (0)	Hematological safety and diagnostic efficacy in patients undergoing neurological investigation by magnetic resonance imaging
DGD-3-21; 1988; France	16-80; 50; 50	3 NR, O, S	0.1 mmol/kg 2.7-6.7 mL/min (give over 3 minutes)	Safety: AEs  Summary: Change in diagnosis in 78% of with change in therapeutic approach in 74%;AEs (0)	Neurological magnetic resonance imaging, general safety and diagnostic efficacy
DGD-3-20; 1988; France	24-72; 48; 48	3 NR, O, S	0.1 mmol/kg Bolus injection	Safety: AEs  Summary: Contrast improved ophthalmologic and ENT pathologies; AEs (14) both immediate and delayed consisting of rashes, discomfort, nausea, heat, palpitations	Magnetic resonance imaging general safety and diagnostic efficacy (ENT and ophthalmologic pathologies)
DGD-3-33; 1994; France, Belgium	21-81; 65; 65	3 NR, O, M	0.3 mmol/kg Not noted	Safety: Vital signs, AEs  Summary: study of brain metastases for evaluation of efficacy using triple dose versus a standard	Evaluation of the diagnostic efficacy and clinical safety of triple dose Dotarem in comparison to the standard dose for

				dose with triple dose useful for detection in 89% of cases compared to standard dose; one change in vital signs noted as significant (BP elevation at 2 hrs, return to normal at 3 hrs); AEs (1)	the detection of brain metastases
DGD-3-34; 1994; France, Switzerland	20-82; 45; 45	2/3 NR, O, M	0.3 mmol/kg Rapid injection	Safety: Lab, vital signs, AEs  Summary: additional dose provided more information; lab with significant changes for small numbers; vital sign significant; changes felt to relate to stress variations; AEs (6)	Evaluation of safety and diagnostic efficacy of triple dose Dotarem in the detection of brain tumors
DGD-3-40; 1999; France, Belgium, Switzerland, Luxembourg	54-88; 59; 59	4 NR, O, M	0.2 mmol/kg 5-13 mL/sec then 20 mL rinse with normal saline	Safety: AEs  Summary: controversial value for early detection of perfusion disorders; AEs (6)	Evaluation of cerebral functional MR imaging with Dotarem in the diagnosis of Alzheimer disease; 4 study groups based on dementia status including normal subjects
DGD-3-44; 2003; France, Germany	18-79; 151; 150	3 NR, O, M	0.1 mmol/kg 1-2 mL/sec	Safety: Vital signs, AEs  Summary: CNS efficacy for sensitivity and specificity did not show significant difference between image sets; vital sign changes and out of	CNS study to confirm the efficacy of Dotarem enhanced MRI to a non enhanced MRI in the characterization of cerebral and spinal tumors

				range values not considered clinically relevant; AEs (15); 7 deaths	using histology as “standard of truth”
DGD-3-15; 1988; France	0.04-17; 29; 29	2 NR, O, S	0.1 mmol/kg 3 mL/min, may dilute in saline or inject undiluted	Safety: Lab (in 20), AEs  Summary: Better or complementary diagnostic contribution with contrasted images in 69% and change in therapeutic management in 34%; lab, 3 subjects with variations not considered statistically or clinically significant; AEs (0)	CNS study for efficacy and safety in children ages 0-18 years
DGD-3-16; 1988; France	0.5-17; 20; 20	2 NR, O, S	0.1 mmol/kg 2.4 mL/min	Safety: AEs  Summary: Better or complementary diagnostic contribution with contrasted images in 94% and change in therapeutic management in 15%; AEs (0)	CNS study for efficacy and safety in children ages 0-18 years
DGD-3-29; 1991; France	1-17; 50; 50	4 NR, O, S	0.1 mmol/kg Rapid bolus	Safety: AEs  Summary: Better or complementary diagnostic contribution with contrasted images in 80% and variable change in therapeutic management in 10% or more; AEs (0)	CNS study for efficacy and safety in children ages 0-18 years
DGD-44-50;	3-95; 402;	3	0.1 mmol/kg	Safety: Lab, vital	Safety and

2010; USA, Latin America, Europe, South Korea	278 Caucasian - 83.0% Asian-11.4% Black-4.7%	R, DB, C, M	2 mL/sec (adults) 1.1 mL/sec (peds)	signs, ECG (100 subjects), AEs  Summary: Lesion characterization and comparison to Magnevist showed contrast enhanced images superior and similar to Magnevist; laboratory and vital sign shifts with no clinically relevant trending; ECGs with a few shifts and abnormalities; AEs (Dotarem 9.6% for adults, Magnevist 13.7%, 21.1% peds, 2 SAEs); no clinically significant changes in peds	efficacy evaluation of Dotarem in magnetic resonance imaging (MRI) in patients with central nervous system (CNS) lesions
DGD-3-02; 1987; France	21-76; 20; 20	2 NR, O, S	0.1 mmol/kg 3.3 mL/min	Safety: Lab, AEs  Summary: Whole body lesion assessment/follow up lesions with good or excellent visualization; lab with minor hematologic variations of no biological significance; AE (1)	Trial conducted for evaluation of bones and soft tissues
DGD-3-13; 1987; France	35-73; 30; 30	3 NR, O, S	0.1 mmol/kg Injection over 1 minute	Safety: AEs  Summary: Hepatic imaging using either 0.2 or 0.4 mL/kg with similar efficacy; AEs(1)	Body imaging with three groups of 10 subjects to evaluate body (liver) images before and after injection
DGD-3-19; 1987; France	20-84; 39; 39	3 NR, O, S	0.1 mmol/kg (18) 0.2 mmol/kg	Safety: AEs  Summary: Image	Body imaging for contribution of imaging to liver

			(21) 3-12 mL/min; rapid IV over 15 sec-1 min	quality unchanged with dose; AEs (0)	lesions before and after injection
DGD-3-22; 1988; France	21-79; 24; 24	3 NR, O, S	0.1 mmol/kg 8-16 mL/min	Safety: AEs  Summary: Better definitions of hepatic lesions after contrast; AEs (6)	Body imaging for subjects with suspected liver disease also undergoing CT and ultrasound exams
DGD-3-26; 1989; France	28-85; 20; 10	4 R, O, S	0.1 mmol/kg Bolus max 2 mL/sec	Safety: Lab, AEs  Summary: Subjects with chronic renal failure had diagnostic quality improved after contrast; lab no significant variations or differences from control; AEs(0)	Diagnostic efficacy of MRI investigation of the kidney without and with Dotarem; 2 parallel groups (injected with either Magnevist or Dotarem)
DGD-3-32; 1994; France, Belgium	37-77; 80; 80	3 NR, O. M	0.1 mmol/kg Bolus <10 sec	Safety: AEs  Summary: Whole body breast imaging may be of value when other studies are equivocal; AEs (0)	Body imaging for diagnostic efficacy of Dotarem for the early diagnosis of breast cancer; patients with known tumors (equivocal diagnosis)
DGD-3-49; 2003; France, Belgium	18-87; 120; 120	3 NR, O, M	0.1 mmol/kg 1.5-3.0 mL/sec mean 2.1 mL/sec	Safety: Vital signs, AEs  Summary: Characterization of focal hepatic lesions with and without Dotarem not statistically significant difference for efficacy but therapeutic management was helped; vital sign	Body MRI with Dotarem in the characterization of focal hepatic lesions

				variations in about 20% but not felt to be clinically relevant; AEs (17); SAEs (2)	
DGD-3-50; 2003; France	26-87; 110; 109	3 NR, O, M	0.1 mmol/kg 1-2 mL/sec followed by 10 mL saline infusion	Safety: Vital signs, AEs  Summary: Study to assess efficacy of imaging with and without contrast using a corroborative diagnosis of biopsy, surgery, or cytology with efficacy results non-conclusive; vital sign changes in 4-13% of subjects but not associated with AEs; AEs (14); SAEs (5, one death)	Body MRI with Dotarem to characterize abdominal and pelvic lesions
DGD-44-44; 2008 France, Belgium, Italy, Spain	22-92; 114; 70	4 NR, O, C, M	0.1 mmol/kg 1.4-2.6 mL/sec	Safety: Lab, vital signs creatinine, eGFR, AEs  Summary: Renal safety in subjects with stable stage III/IV renal insufficiency comparing creatinine and eGFR values to baseline in subjects who received Dotarem and subjects who did not receive Dotarem with 1 Dotarem nephrotoxic reaction: no significant differences in lab or vital signs with chronically abnormal values at baseline and post imaging	Renal safety evaluation after Dotarem enhanced MRI compared with non enhanced MRI in patients at high risk for developing contrast medium induced nephropathy

				except for bicarbonate post imaging; clinically significant but chronically typical abnormalities ranging from 0.9% for sodium to 27.2% for uric acid; AEs (6)	
DGD-3-36; 1998; France	24-84; 41; 41	3 NR, O, M	0.1 mmol/kg 2 mL/sec followed by 20 mL normal saline at 2 mL/sec	Safety: AEs  Summary: MRA for renal artery stenosis, satisfactory sensitivity and specificity; AEs(0)	MRA to assess efficacy of Dotarem for renal artery stenosis when compared to DSA
DGD-3-37; 1998; France, Austria	27-89; 35; 35	3 R, SB, S	0.05 or 0.1 mmol/kg 1-2 mL/sec followed by 20 mL normal saline at 2 mL/sec	Safety: AEs  Summary: No dose differences, Dotarem results improved over scintigraphy and exam time decreased from DSA; AEs (3 allergic)	Sensitivity and specificity for diagnosis of pulmonary embolism at 0.05 and 0.1 mmol/kg
DGD-3-38; 1998; Switzerland, Belgium	55-81; 40; 40 Caucasian- 88% Black-10% Hispanic-2%	3 NR, O, M	0.1 mmol/kg 2 mL/sec followed by infusion of 20 mL normal saline at 3 mL/sec	Safety: AEs  Summary: sensitivity and specificity similar between uncontrasted and contrast studies but more assessable segments with contrast; AEs(0)	Comparison of MRA to DSA for carotid artery stenosis
DGD-3-39; 1998; France, Austria	35-84; 40; 40	3 R, SB, M	0.05 or 0.1 mmol/kg 2 mL/min followed by 20 mL normal saline "chaser"	Safety: AEs  Summary: No significant difference between doses, high specificity and low sensitivity; AEs (0)	MRA sensitivity and specificity of Dotarem for stenosis lower limb arteries compared to DSA
DGD-3-42; 2004;	31-72; 6; 6	4 NR, O,	0.125 or 0.250 mmol/kg	Safety: AEs	Evaluation of Dotarem

The Netherlands		S	2 mL/sec followed by 20 mL saline infusion at 2 mL/ sec	Summary: MRA for non coronary arterial disease compared with x- ray angiography showed higher accuracy with Dotarem MRA; AEs (0)	enhanced MRA compared to time of flight MRA in the diagnosis of clinically significant non-coronary arterial disease
DGD-44-38; 2006; USA	25-87; 100; 100	3 NR, O, M	0.1 mmol/kg 1-2 mL/sec	Safety: Vital signs, AEs Summary: Higher accuracy with Dotarem MRA compared to DSA; vital signs changes not considered significant or clinically relevant; AEs (14); SAE (1)	Evaluation of Dotarem enhanced MRA compared to time of flight MRA in the diagnosis of clinically significant non-coronary arterial disease
DGD-44-42; 2008; South Korea	21-86; 92; 92	4 NR, O, S	0.1 mmol/kg 1-2 mL/sec	Safety: Vital signs, adverse events  Summary: Higher accuracy with Dotarem MRA; vital signs, few out of range with one increase in SBP an SAE; AEs (6)	Evaluation of Dotarem enhanced MRA compared to time of flight MRA in the diagnosis of clinically significant non-coronary arterial disease
DGD-44-46; 2009; USA	23-85; 33; 33 Caucasian-70% Black-27% Asian-3%	3 NR, O, M	0.1 mmol/kg 2 mL/sec	Safety: Lab, vital signs, AEs  Summary: Premature termination of study, no efficacy analysis; lab (4) and vital sign changes either not clinically significant or chronically typical. not study related; AEs (9)	Comparison of MRA TOF images and Dotarem images with CTA (renal arterial disease)
DGD-44-47; 2009; USA,	26-80; 13; 13 Caucasian-	3 NR, O, M	0.1 mmol/kg 1-3 mL/sec	Safety: Lab, vital signs, AEs	Comparison of MRA TOF images and Dotarem

Canada	92% Other-8%			Summary: Premature termination of study, no efficacy analysis; lab and vital sign changes either not clinically significant or chronically typical; AEs (5)	images with CTA (renal arterial disease)
DGD-44-48; 2009; USA, Columbia, Argentina, Mexico, South Korea, Chile	20-97; 222; 222 Caucasian-62% Black-5% Asian-18% Other-14%	3/4 NR, O, M	0.1 mmol/kg 2 mL/sec	Safety: Lab, vital signs, AEs Summary: Decreased technical failure rate with Dotarem and non inferior specificity but no significant difference in sensitivity; lab and vital signs with mild/moderate biochemistry/hematology abnormalities not felt to be related and no clinically significant vital sign changes, a few changes noted as AEs; AEs (27)	Comparison of MRA TOF images and Dotarem images with CTA (cervical artery disease)
DGD-44-49; 2009; USA, South Africa, Argentina, Mexico, South Korea, Chile	21-87; 211; 211 Caucasian-68% Black-6% Asian-15%	3/4 NR, O, M	0.1 mmol/kg 2 mL/sec	Safety: Lab, vital signs, AEs  Summary: Decreased technical failure rate with Dotarem and non inferior specificity but no significant difference in sensitivity; lab and vital signs with a few changes noted as AEs, one hypersensitivity and 3 administration site	Comparison of MRA TOF images and Dotarem images with CTA (cervical artery disease)

				conditions, 2 biochemistry abnormalities AEs (18); SAEs (1 Dotarem)	
DGD-44-45; 2010; Austria, Germany, France, Italy, Spain	24-91; 189; 92	3/4 R, DB, C, M	0.1 mmol/kg 1 mL/sec	Safety: Vital signs, AEs  Summary: Agreement between Dotarem and Gadovist to DSA with non inferiority of Dotarem to Gadovist; vital sign variations similar to comparator and not clinically significant; AEs (4), did not include 1 injection site event	Comparison of Dotarem enhanced MRA to Gadovist enhanced MRA in the diagnosis of clinically significant abdominal or lower limb arterial disease
DGD-44-52; 2009; Germany	45-77; 20; 20	4 R, DB, C, S	0.1 mmol/kg 1 mL/sec followed by 25-30 mL normal saline flush	Safety: AEs  Summary: Diagnostic performance similar; vital signs for one subject BP out of range BP during the second MRA but not clinically abnormal; AEs (0)	Comparison of Dotarem enhanced MRA to Gadovist enhanced MRA in the diagnosis of clinically significant abdominal or lower limb arterial disease
<b>Total Subjects N = 2813</b>					

C : Comparative; S: Single center; M: Multicenter; O: Open; DB: Double Blind; NR: Not Randomized; R: Randomized

As noted in the table, most studies conducted were single center, open label, non randomized studies.

Table 30 below summarizes the demographics of sex, age, and ethnicity for all pooled trials, CNS trials, pivotal trials, and comparator trials analyses.

**Table 30: Demographic Variables, All Studies, CNS Studies, Pivotal Trials**

		<b>Dotarem N = 2813</b>	<b>CNS Studies N = 1329</b>	<b>Pivotal Trials Dotarem* N = 428</b>	<b>Gadolinium Comparator N = 371</b>
<b>Sex</b>	Male	1532 (54.5%)	687 (51.7%)	212 (49.5%)	197(53.1%)
	Female	1274 (45.3%)	636 (47.9%)	216 (50.5%)	174 (46.9%)
<b>Age</b>	Mean	53.7	46.1	49.6	54.2
	Min, Max	0.1, 97.0	0.1, 88.0	2.9/85.1	17.0, 94.4
<b>Race</b>	Caucasian	1181 (74.4%)	479 (90.0%)	375 (87.6%)	94(80.3%)
	Black	64 (4.0%)	18 (3.4%)	18 (4.2%)	7 (6.0%)
	Asian	189 (11.9%)	27 (5.1%)	27 (6.3%)	15 (12.8%)
	Other	153 (9.6%)	8 (1.5%)	8 (1.9%)	1 (0.9%)
<b>Weight</b>	Mean	69.1 kg	65.3 kg	71.5 kg	72.2 kg
	Min, Max	2.7 kg, 147.0 kg	2.7 kg, 136.0 kg	13.0/136.0 kg	42.0 kg, 135.4 kg

\* Magnevist demographics for the CNS trials, ( N = 117), were similar for sex, age, and weight; there were less Caucasians and more Blacks and Asians that received Magnevist

Sex, age, and weight demographics were similar for the pooled analyses and for the comparator gadolinium group. The race demographics of the trials were reflective of the demographics of the country in which the trial was performed as has also been noted for the US IND studies listed in Table 29. For baseline demographics for the pediatric population subgrouped by age, there were approximately 55% males and 45% females in all age groups. Race was not collected for any subjects in the under age 2 group or for 96 subjects in the 2-17 age group. Approximately 20% of subjects where race was collected were Caucasian. The Black population ranged between 4.7% to 9.1%, there were no Asians listed as pediatric subjects, and there were a total number of 3 subjects listed as Other.

### 7.2.2 Explorations for Dose Response

The applicant did not conduct any dose ranging studies to provide information relevant for dosing recommendations of Dotarem.

### 7.2.3 Special Animal and/or In Vitro Testing

The results of the non-clinical studies indicate that Dotarem is an effective agent for MRI. It was generally well tolerated in non-clinical pharmacology and toxicology studies and studies conducted on safety pharmacology did not yield results suggestive of concern for the proposed single use dose in humans.

Dotarem behaved similarly to other agents in its class. Following intravenous injection, Dotarem was rapidly distributed throughout the whole body, primarily in the extracellular space, without restriction except that it did not cross the blood brain barrier. It was rapidly and almost exclusively eliminated in the urine. Dose proportional pharmacokinetics were observed in rats, rabbits, and in dogs. No protein binding and no metabolism was noted. In pre clinical studies, negligible amount crossed the placenta and a negligible amount was excreted into milk. It is not known whether Dotarem is excreted into human milk.

Single and repeated IV administrations of Dotarem to mice, rats, and dogs were generally well tolerated with mild clinical signs noted such as minor proconvulsant activity at high IV dose levels in mice and high intracisternal dose level in rats. In dogs, there were moderate and transient effects on cardiovascular and hemodynamic patterns attributed mostly to osmolality and high injected volume with no adverse effects of Dotarem on the ECGs. There was vacuolization of renal proximal tubular cells and upper tract urothelium with partial reversibility after the 4 week treatment period to rats and dogs and minor changes only in glomerular and tubular function when administered at high doses.

No juvenile pharm/tox studies were conducted. No teratogenic, embryo toxicity, or fetal toxicity effects were noted.

Overall, the non-clinical pharmacology, toxicology, and absorption, distribution, metabolism, and excretion studies conducted with Dotarem did not yield any results of concern for single dose use in humans.

#### 7.2.4 Routine Clinical Testing

The routine clinical testing of subjects was adequate when comprehensive laboratory and vital sign evaluations were performed but was limited based on the numbers of subjects receiving this complete evaluation. Safety and tolerability of Dotarem was evaluated in clinical studies by means of physical exam, AEs, laboratory parameters, and vital sign measurement.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

During clinical development, both a non compartmental model and an open two compartment model, were used for the analysis of plasma and urine concentrations. They provided similar results. The results of the PK analysis indicated that the kinetics of Dotarem conform to a one compartment open model and that they were linear and proportional to dose. The mean elimination half life was  $1.4 \pm 0.2$  hr in female subjects and  $2.0 \pm 0.7$  hr in male subjects. After injection, Dotarem was distributed predominantly in the extracellular space. Elimination was by glomerular filtration.

$72.9\% \pm 17.0\%$  and  $85.4 \pm 9.7\%$  was eliminated after 48 hours in female and male subjects respectively with similar values after a cumulative dose of 0.3 mmol/kg bw. Dotarem is not metabolized and is excreted unchanged. According to the applicant, Dotarem has no effect on the zinc or iron metabolism.

The applicant conducted no placebo studies and studies in population groups such as age, gender, and race studies were limited. Ethnic differences in the pharmacokinetics of Dotarem were not studied but no race effect is expected due to the lack of protein binding and metabolism. The pharmacokinetics of Dotarem was not studied in the pediatric population. Age was not studied. Gender had no relevant difference effect on the pharmacokinetics of Dotarem. Hepatic impairment was not studied but no effect is expected due to the lack of metabolism. Elimination is proportionately decreased with the degree of renal impairment.

Safety was evaluated for several special groups and situations based on subject enrollment characteristics by history, to include renal disease, hepatic disease, cardiac disease, diabetes, allergic history, and history of allergy to contrast agents. Comparing enrollment for the all subjects, CNS studies, and pivotal trials categories, apart for the subgroup contrast allergy, the percent of subjects with a positive disease history was less for the CNS and pivotal trials which is expected based on concomitant factors such as medical conditions in patients with vascular disease who would be referred for an MRA study. Enrollment of subjects with a history of contrast allergy was 1.8%, 1.6%, and 1.9% for these groups respectively. Subjects enrolled in the clinical trials that received comparator drugs had underlying medical conditions similar to the all subjects category.

To evaluate these groups, the applicant compared the AE rate for subjects both with and without a history of the disease for both Dotarem and the comparator drug. Approximately 66% of subjects overall received a dose of Dotarem or comparator at 0.05-0.1 mmol/kg. 43.8% of all subjects received the theoretical dose with 43.1% receiving the dose at the theoretical rate of injection versus 55.8% and 54.2% for these same variables for comparator drug. 91.4% of subjects in the two pivotal CNS trials received the 0.05-0.1 mmol/kg dose.

The applicant analyzed the previous noted pooled samples. Quantitative variables were described in terms of frequency and percentage of individuals examined with pooled subgroup analyses for subjects with and without disease. Study region was used as a cofactor in the regression model for the -050 study only based on lack of influence on the results of this study. In general, the demographics for subjects with and without disease were comparable between Dotarem and comparator drugs although for renal disease, a greater percentage of subjects received Dotarem. The AE rate overall as well as for related AEs was also generally comparable with no trending noted. For both Dotarem and comparator, the AE rate was higher for subjects with renal disease, hepatic disease, and subjects with an allergic history and was lower for subjects with a history of cardiovascular disease or a history of diabetes.

*Reviewer's Comment: Although the applicant did not conduct special studies such as for age and gender and for hepatic impairment, the overall AE profile in subjects with pre existing conditions was similar for Dotarem and approved comparator drugs.*

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

371 subjects in clinical trials were injected with comparator gadolinium drugs. The reported incidence of adverse events after administration with Dotarem is similar to other drugs in this class. The types of AEs by SOC and PT are also similar. To date, no cases of unconfounded nephrogenic sclerosing fibrosis, (NSF), a serious AE, have been reported.

### 7.3 Major Safety Results

A comprehensive safety summary is considered for the two pivotal trials, DGD-44-050 and DGD-3-44. Other portions of this review address safety as pooled analyses for all clinical trials and for the 23 CNS clinical trials.

DGD-44-050 was conducted under SPA and evaluated agreed upon safety parameters. Subjects underwent a medical history at the time of screening. A urine pregnancy test was performed if needed within 24 hours prior to the MRI exams. The imaging examinations were then scheduled. Safety assessments included adverse events profile, injection-site tolerance, vital signs, hematology and biochemistry tests, and routine urinalysis. In addition, ECG monitoring was conducted prior to MRI and within 30 minutes post injection on the first 100 patients enrolled in the US study population with measurements to include QT and QT<sub>bazett</sub> and QT<sub>fredericia</sub>.

For this study, a total of 395 subjects were evaluated for safety, 240 adults who received Dotarem, 38 pediatric subjects who received Dotarem, and 117 adults who received Magnevist. Mean adult dose for both arms was 0.1 mmol/kg ± 0.05 mmol/kg bw with a mean injection rate of 2 mL/sec. Mean pediatric dose was the same as for adults with a mean injection rate of 1.1 mL/sec. 5 adults, (3 Dotarem and 2 Magnevist) were considered not dose compliant.

Treatment emergent AEs were reported in 9.6% of Dotarem adult subjects and 13.7% of Magnevist subjects and 21.1% of pediatric subjects. Those events considered as drug related were 3.8%, 7.7%, and 15.8% respectively.

Administration site conditions/systemic inflammatory response/chest pain were reported in 2.5% of adults who received Dotarem as versus 6.8% of subjects who received Magnevist and 2.6% of pediatric subjects. Injection site reactions consisting of pain, burning, inflammation, or skin eruption were infrequent in any of the three groups. No hypersensitivity allergic reactions were reported for any of the subjects. 2 adults and 2 pediatric subjects who received Dotarem (no Magnevist subjects) had nausea or vomiting, (0.8% of adults, 5.3% of pediatric subjects) and one adult in the Dotarem group had diarrhea. Two pediatric subjects experienced headache, (5.3%). Most adverse events were mild or moderate in intensity, transient in nature, and occurred immediately or within 48 hours following Dotarem administration. 103 patients (3.6%) experienced at least one adverse event that was considered related to Dotarem.

No deaths occurred. One adult who received Magnevist and one child experienced SAEs considered to be not related to treatment.

When baseline pre treatment hematology/biochemistry laboratory parameters, urinalysis, and vital signs were compared to 24 hour values, there were no clinically relevant trends or clinically significant changes in any of the three groups. There were small and equivalent increases in mean QTc for all three groups when baseline values were compared to those at 30 minutes post injection. Three Dotarem adults and two pediatric subjects experienced a shift from normal to abnormal ECG about 30 minutes after treatment to include 2 subjects with a slight increase in QTcB however no subjects

experienced an increase >460 msec or an increase in QTcB from baseline of >15 ms and no subjects had an abnormal QTcF per the pre defined maximum of 450 msec.

150 subjects enrolled in the DGD-3-44 clinical trial were injected with Dotarem and included in the safety analysis. Most subjects received the 0.1 mmol/kg dose of Dotarem at a rate of 2 mL/sec. The minimum/maximum dose ranged from 0.1-0.15 mmol/kg. 11 subjects (7.3%) experienced a total of 15 adverse events. 8 events were considered severe cardiovascular disorders, 2 were related to pre-existing tumor disease, 3 were related to injection site (burning and coolness), and 2 were digestive and general disorders of nausea and vertigo. 9 of the 15 adverse events were reported as SAEs not related to Dotarem. These SAEs led to the death of 7 subjects that was assessed as related to subjects' underlying diseases and general poor condition. One SAE of pulmonary embolism (and subject death) led to subject withdrawal. Post treatment adverse events were listed in the study report with each constituting a single event with 6.7% incidence. By PT listing, several events such as brain hemorrhage were obviously related to the subject's underlying medical condition. 66.6% of these events were considered severe as would be anticipated for the subject's underlying condition. Only 4 injection site reactions were considered related to Dotarem and these were considered as mild or moderate reactions. Injection site reactions noted occurred within 30 minutes after injection and were of 5 minutes duration or less. As already noted, for 9 AEs the outcome was death and 1 AE led to subject withdrawal.

This reviewer evaluated the subject narratives for the SAEs and deaths and concurs that they were not related to Dotarem. Brief summaries are presented below:

- Subject 06001: A 64 year old male with a medical history that included right lung lobectomy, CNS tumor, and hypertension experienced neurological symptoms and hemodynamic instability 20 days after Dotarem injection and subsequently died secondary to heart failure
- Subject 06005: A 48 year old male with a history of craniopharyngioma and symptomatic hydrocephalus had cerebral cyst opacification under general anesthesia the day after Dotarem injection and experienced episodes of desaturation and tachyarrhythmia followed by an edematous right limb and death which was attributed to pulmonary embolism secondary to phlebitis
- Subject 02012: A 52 year old male with a brain tumor in the "right ventricular crossing" with symptoms of gait and memory disorder was found dead in his bed 7 days after Dotarem injection attributed to either thrombophlebitis or brain hemorrhage
- Subject 08005: A 72 year old male with a history of hypertension and metastatic lung cancer experienced an increase in intracranial pressure 27 days after injection of Dotarem, was hospitalized but continued to deteriorate and died over 3 weeks after hospitalization
- Subject 10001: An 18 year old female with a history of craniopharyngioma underwent neurosurgery 8 days after Dotarem exam, then 25 days post Dotarem

injection experienced arterial vasospasm and cerebral edema which was demonstrated by CT scan and arteriography, with no resolution noted and death 3 weeks post Dotarem exam

- Subject 01017: A 40 year old female with a left temporal meningioma underwent surgical resection 8 days after Dotarem exam then experienced cerebral edema and cerebral ischemia of the middle cerebral artery right after surgery followed by death 2 days later
- Subject 03029: A 55 year old subject with metastatic colon cancer experienced general aggravation of her condition 7 days after Dotarem injection and continued to deteriorate with death one week after Dotarem attributed to metastatic disease with carcinomatous meningitis

Clinical trial safety monitors for this study consisted of AE and vital sign evaluation. The vital sign assessments are discussed in section 7.4.3 of this review.

This reviewer noted that the protocol defined safety monitoring was pre injection, immediately after injection, then at 5 minutes, 15 minutes, 1 hour, 2 hours, 24 hours, 48 hours, and 72 hours. All 151 subjects presented for AE evaluation at the time points before 24 hours. At 24, 48, and 72 hours, that same group of subjects decreased to 84.1%, 64.2%, and 49.7%. According to the applicant (Response to FDA Clinical Request 6 dated 12-19-12), the percent was the same regardless of whether subjects were assessed at all of the prior time points. Possibly this was secondary to the manner of AE assessment which might have been done by telephone as versus vital sign evaluation where the numbers were less which would require an in person visit. The applicant's conclusion regarding AEs and vital sign evaluation was that data from the AEs did not induce any AE reporting.

This reviewer concluded that the safety profile based on the two pivotal trials was similar to the 49 clinical trials.

### 7.3.1 Deaths

There were 8 deaths reported in the Dotarem group of the total 2813 subjects. The narratives for 7 of these (study DGD-3-44) were reported in section 7.3 safety results which considered the 2 pivotal trials. The additional narrative follows:

Subject 05001 (Study DGD-3-50): A 75 year old man with a history of cardiovascular disease, hepatic disease, and pancreatic tumor received Dotarem for a tumoral workup then 12 days after administration of Dotarem, he developed cardiac failure and died.

As was noted for the other deaths, there was no causal relationship to Dotarem.

### 7.3.2 Nonfatal Serious Adverse Events

23 subjects including a 5 year old child experienced SAEs. The child has a history of chronic respiratory and a CNS tumor and developed hypoxia 1 day after receiving Dotarem. Narratives for the 2 subjects who experienced SAEs related to Dotarem are included below:

- Subject 7004 (Study DGD-44-049): A 53 year old male experienced a hypersensitivity reaction of lightheadedness, chest tightness, coughing, and itching approximately 15 minutes after receiving Dotarem and was medically treated and hospitalized for an allergic reaction
- Subject 10007 (Study DGD-44-049): A 60 year old female with a history of renal insufficiency (baseline creatinine 1.09 mg/dL) and carotid stenosis experienced acute renal failure approximately 21 hours after injection of Dotarem with creatinine increased to 1.2 mg/dL that was elevated further to 1.27 mg/dL in 9 days but then decreased to 1.20 mg/dL about a month after Dotarem with moderate renal failure consider the sequelae of Dotarem injection

Both of these SAEs are listed events for other agents in the class and will be listed for Dotarem.

### 7.3.3 Dropouts and/or Discontinuations

Subjects who did not receive any study drug were considered as dropouts. For the clinical population, there were 21 withdrawals, (0.7%) from the Dotarem group and 7, (1.9%) from the comparator gadolinium group. Most were for reasons not related to study drug such as technical factors, loss to follow up, or withdrawal of consent. Only a single subject, a subject in the Dotarem group, withdrew secondary to an AE, (an SAE). Section 6.1.3, Table 12 of the efficacy review lists the withdrawals and discontinuations for the two pivotal trials. Subject 06005 was enrolled in study DGD-3-44. See section 7.3 safety for the narrative of this SAE.

Based on the above subject data for all subjects studied, the conclusion is that discontinuation due to study drug AEs is not a significant issue.

#### 7.3.4 Significant Adverse Events

The majority of the reported adverse events are consistent with those observed with other gadolinium based contrast agents and will be discussed as common adverse events, section 7.4.1. 29 or (8.0%) of Dotarem AEs were serious with 1 SAE (1.4%) for comparator. Rare anaphylactoid reactions have been noted with an incidence of < 1/1000. 8 subject deaths occurred in clinical trials. These are discussed in section 7.3.1.

#### 7.3.5 Submission Specific Primary Safety Concerns

**After assessment of the safety monitoring and safety data provided by the applicant, this reviewer concluded that drug development lacked appropriate safety monitoring. Safety monitoring for the clinical trials overall was generally insufficient but appears adequate for the -050 CNS study and 4 MRA studies that were conducted under US IND. This concern has been addressed in section 7.2 adequacy of safety assessments.**

**A second concern which is addressed in section 7.7 relates to safety in children under age 2. Because of immature renal function, the safety profile requires a complete evaluation. In this regard, PK studies were not conducted in this population and laboratory evaluations were performed for only 2 subjects. There were no studies in any pediatric age group to assess for gadolinium excretion in the urine.**

### 7.4 Supportive Safety Results

#### 7.4.1 Common Adverse Events

Adverse reactions, mostly minor, have been noted in 263 (9.3%) of subjects (at least one AE) and consist of general disorders and administration site conditions (mainly injection site coldness, feeling hot or cold, and injection site pain), nervous system disorders (headache and dizziness), gastrointestinal system disorders (nausea), and respiratory, thoracic, and mediastinal disorders (sneezing, wheezing, yawning). 3.9% of AEs were considered to be related to treatment. For drug related AEs, nausea (18

subjects, 0.6%), headache (13 subjects, 0.5%), injection site pain (11 subjects, 0.4%), and feeling hot/cold (9 subjects, 0.3%) were most common. Similar AEs were reported for comparator drugs but with varying percents. 87.4% of all Dotarem AEs were either mild or moderate with 87.1% of comparator AEs either mild or moderate.

Table 31 lists drug related adverse events by SOC and PT reported for a  $\geq 0.5\%$  incidence in all clinical trials.

**Table 31: Drug Related Adverse Events Reported With a Frequency of  $\geq 0.5\%$  of The Primary Safety Database in Clinical Trial Subjects**

<b>Primary System Organ Class and Preferred Term</b>	<b>Number (% Incidence) Dotarem/Comparator</b>
<b>Phase 1-4 Total</b>	Total number of subjects = 2813 (100%) Total number of events = 363 (100%) Total number of subjects with any drug related event = 111 (3.9%) Number of drug related events = 29 (8.0%)
<b>Comparator Total</b>	Total number of subjects = 371 (100%) Total number of events = 70 (100%) Total number of subjects with any drug related event = 51 (%) Number of drug related events = 36 (9.7%)
<b>Gastrointestinal disorders</b> Nausea	27 (1.0%)/7 (1.9%) 18 (0.6%)/4 (1.1%)
<b>General disorders and administration site conditions</b> Feeling hot or cold Injection site pain	47 (1.7%)/13 (3.5%) 9 (0.3%)/3 (0.8%) 11 (0.4%)/5 (1.3%)
<b>Nervous system disorders</b> Headache Dizziness	31 (1.1%)/17 (4.6%) 13 (0.5%)/16 (4.3%) 0 (0.0%)/1 (0.7%)
<b>Respiratory, thoracic and mediastinal disorders</b> Sneezing Wheezing Yawning	4 (0.1%)/3 (0.8%) 1 (0.0%)/1 (0.3%) 0 (0.0%)/1 (0.3%) 0 (0.0%)/1 (0.3%)

When dose was considered, there was no definite dose effect on the AE rate. As has already mentioned in the safety summary, (section 7), the AE rate and the types of AEs were similar for the CNS studies and the pivotal trials with minor variance for the pediatric population.

This reviewer concurs with the applicant that the safety profile of Dotarem is similar to other approved GBCAs.

#### 7. 4.2 Laboratory Findings

Laboratory parameters were examined at baseline, (pre-dose), and at various time points post injection, up to 72 hours depending on the study. Subject evaluations included clinical chemistry, hematology, and urinalysis. As noted in Table 24, only 31 % of subjects received comprehensive laboratory and vital sign evaluations. An individual summary of the clinical and hematology parameters and time points for assessment is noted in Table 30 which is reproduced from the applicant's Response to Filing Communication to the FDA dated January 6, 2013. These parameters are also summarized in Table 27 which includes a summary, by study, of all safety parameters.

**Table 32: Dotarem Safety, Summary of Laboratory & Hematologic Assessments**

Study	Imaging Indication	Results	Total No. Dotarem Treated Patients	Hematology	Biochemistry
DGD-44-050	CNS	No clinically relevant trends in mean hematology/biochemistry laboratory parameters were apparent in adult patients and no pediatric patients had clinically significant changes.	278	T0, T0+24(±4)h	T0, T0+24(±4)h
DGD-44-049	MRA	No clinically significant laboratory abnormalities occurred, other than those reported as AEs by the investigator. 2 patients had mild biochemistry abnormalities following Dotarem administration, both of which were considered not-related.	187	T0, T0+24(±4)h	T0, T0+24 (±4)h
DGD-44-048	MRA	No clinically significant laboratory abnormalities occurred, other than those reported as AEs by the investigator. 5 patients had biochemistry/hematology abnormalities following Dotarem administration, all of which were mild to moderate and none of which were considered related.	200	T0, T0+24(±4) h	T0, T0+24(±4)h
DGD-44-047	MRA	No clinically significant laboratory abnormalities occurred.	10	T0, T0+24(±4)h	T0, T0+24(±4) h
DGD-44-046	MRA	3 patients had biochemistry abnormalities 1 patient had hematological abnormalities None of these events were considered related to study treatment.	32	T0, T0+24(±4)h	T0, T0+24(±4)h
DGD-44-44	Various	Abnormalities were reported in all parameters at both baseline and post-imaging (frequencies ranging from 8.8% to 56.1% of patients), but were not reported at significantly different rates in the 2 groups, other than post imaging values for bicarbonate (22.9% of Dotarem patients vs. 45.5% of unenhanced patients; p<0.001). Clinically significant but chronically typical abnormalities were reported in frequencies ranging from 0.9% for sodium to 27.2 % for uric acid.	70	To, T0+72 h	To,T0+72 h
DGD-44-039	Cardiac Disorders	There were no relevant changes from baseline in any laboratory parameters assessed.	40	T0, T0+24h	T0, T0+24h

Study	Imaging Indication	Results	Total No. Dotarem Treated Patients	Hematology	Biochemistry
DGD-3-1	CNS	No significant variation in parameters observed apart from blood glucose (at 2 hours, this variation was very moderate and attributable to postprandial values).	10	Not collected	T0, T0 + 2 h, T0 + 24 h
DGD-3-2	Musculo-skeletal	No clinically significant laboratory abnormalities occurred	20	T0, T0 + 4 h, T0 + 24 h	Not collected
DGD-3-3	CNS	Seven of the 15 hematological parameters showed a statistically significant variation of no biological significance.	30	T0, T0+2 h, T0+9 h, T0+24 h	Not collected
DGD-3-4	CNS	Few laboratory parameters showed statistically significant variations but without any clinical significance.	20	T0, T0 + 24 h	T0, T0 + 24 h
DGD-3-5	CNS	Two parameters (calcium and platelets) showed statistically significant variation but of mild intensity without any biological significance. Urinary parameters were not modified.	10	T0, T0+2 h, T0 + 24 h	T0, T0+2 h, T0 + 24 h
DGD-3-6	PK	No clinically significant laboratory abnormality was detected.	6	T0, T0+4.5 h, T0+24h, T0+48h	T0, T0+4.5 h, T0+24h, T0+48h
DGD-3-9	CNS	Laboratory variations were always minor and with no clinical significance.	22	T0, T0 + 2 h, T0 + 24 h	T0, T0 + 2 h, T0 + 24 h
DGD-3-11	CNS	No variation in the clotting parameters was demonstrated.	19	Not collected	T0, T0 + 3 min, T0 + 1 h
DGD-3-15	CNS	No changes in the 17 blood parameters.	29 (children)	T0, T0 + 2 h, T0 + 24 h	T0, T0 + 2 h, T0 + 24 h
DGD-3-17	CNS	No difference observed between the 2 groups for blood parameters.	10	Not collected	At T0, T0+1 h, T0+24 h
DGD-3-26	Kidney/ Renal Failure	No significant difference was found between the control group and the Dotarem group concerning variations in the 24 laboratory parameters considered.	10	T0, T0+24 h, T0+48 h	T0, T0+24 h, T0+48 h
DGD-3-28	PK/ Renal Failure	No clinically significant laboratory abnormality was detected.	12	T0, T0+24 h, T0+48 h, T0+72h	T0, T0+24 h, T0+48 h, T0+72h
DGD-3-34	CNS	The use of a triple dose was very well tolerated in terms of effects on clinical and laboratory parameters.	45	T0, T0+24h	T0, T0+24h
DGD-3-48	PK	There were no relevant changes from baseline in any laboratory parameters assessed.	32	T0, T0+48h	T0, T0+48h

**No laboratory evaluations were performed for study DGD-3-44. More detailed evaluation of laboratory parameters for the -050 study may be summarized as follows:**

**Hematology parameters at 0 and 24 hours for similar for both Dotarem and Magnevist showing subjects with clinically significant values as secondary to underlying medical conditions with up to 25% of adults with clinically significant hematology parameters of chronic disease**

**For the pediatric population there were no clinically significant hematologic abnormalities which were not chronically typical at 0 and 24 hours even values were significant**

**Biochemical parameters for liver and renal function were similar for Dotarem and Magnevist apart from 1 subject who was noted to have a chronically abnormal creatinine value, 4 Dotarem subjects and 1 Magnevist subject who had clinically significant glucose values at 24 hours**

**A few clinically significant but chronically typical biochemical abnormal values were noted in the pediatric population**

**UA as evaluated by dipstick was abnormal for 50% of all groups and 6 Dotarem adults, 1 Magnevist adult, and 1 pediatric subject had clinically significant change at 24 hours.**

**As was noted for vital signs evaluations and as has already been noted as a limitation of clinical trial safety monitoring, the numbers of subjects receiving comprehensive laboratoring monitoring was insufficient, particularly the pediatric group under age 2. As a summary statement, this reviewer noted that laboratory evaluations which included blood cell counts, (with differential count), serum chemistry and special serum markers, electrolytes, clotting parameters, and urine parameters and which were evaluated pre injection then post injection at intervals up to 72 hours showed few significant variations. Significant variations were usually not considered to be relevant or clinically significant or were considered chronically typical. No substantial changes were noted in the pediatric population from baseline to follow up.**

#### 7.4.3 Vital Signs

The assessment of vital signs and laboratory parameters was the investigator's responsibility. If any individual values or changes from baseline were clinically significant for a given subject, these abnormalities had to be reported as adverse events. Vital signs were not assessed for the CNS studies apart from the two pivotal

trials. They were assessed for the 3 PK studies and for the phase 2 cardiac safety study, for the phase 3 and phase 4 body studies, and for most MRA studies. A total of 867 subjects, (31%) were monitored by laboratory parameters and vital signs with an additional 680 subjects, (total 1547 or 55%) monitored by vital signs.

The applicant noted that Guerbet has pre-defined ranges for the vitals signs and variations and provided these on 12-19-12 in response to a clinical request. The values and variations used are reported as Table 33 in this review, Tables 6 and 7 taken from the response.

**Table 33: Pre Defined Ranges for Vital Signs and Ranges of Variation**

**Table 6: Pre-Defined Value Ranges for Vital Signs to Avoid Absurd Values**

	Units	Adults (*)		Children (**)	
		Min	Vital Sign Range Max	Min	Vital Sign Range Max
SBP (supine blood pressure)	mmHg	50	200	50	160
DBP (diastolic blood pressure)	mmHg	40	110	20	100
Heart Rate	beats/min	50	200	50	160

(\*) Korea: age >=20 years , other countries: age >= 18 years

(\*\*) Korea: age < 20 years, other countries: age < 18 years

**Table 7: Vital Signs Variations from Baseline, Pre-Defined Ranges for Variations**

	Units	Adults (*)		Children (**)	
		Delta Min	Delta Max	Delta Min	Delta Max
SBP (supine blood pressure)	mmHg	-20	+30	-20	+20
DBP (diastolic blood pressure)	mmHg	-15	+30	-15	+20
Heart Rate	beats/min	-20	+20	-20	+20

(\*) Korea: age >=20 years; other countries: age >= 18 years

(\*\*) Korea: age < 20 years, other countries: age < 18 years

As noted in these tables, For systolic blood pressure, (SBP), an increase of 30 or decrease of more than 20 mm Hg for adults and increase or decrease of more than 20 for children compared to the value measured prior to injection of contrast medium was considered a relevant change. For changes in diastolic blood pressure, (DBP), changes of more than 30 mm increase for adults and 20 mm increase for children and decreases of more than 15 mm for both categories 15 mm Hg were considered relevant. With respect to pulse, an increase or a decrease of >20 beats per minute, (bpm), for either adults or children was considered as a relevant change to the value measured prior to

injection of contrast medium. Although the pre defined ranges provided are considered acceptable minimums by this reviewer, the maximum ranges appear high but were probably acceptable as subjects were questioned for a history of cardiovascular disease prior to injection of contrast media. For purposes of safety analysis, vital signs were reported as results for individual studies. The applicant did not conduct any pooled analyses or demographic analyses. No summary shift tables were presented.

Results from the two CNS pivotal trials, DGD-3-44 and DGD-44-050 will be discussed first. According to the protocol, vital sign (and AE) assessment for the DGD-3-44 study was scheduled just before contrast injection, just after injection, after 5 minutes, at 15 minutes, at 1 hour, at 2 hours, at 24 hours, at 48 hours, and at 72 hours. According to the applicant (response to clinical request dated 12-19-12), only 94% of subjects were evaluated at all the pre-specified points up to the two hour interval. For this group where vital signs were assessed at all initial time points, vital sign evaluation was for only 72.2% at 24 hours, 54.3% at 48 hours, and 37.7% at 72 hours. The overall percent followed up at these intervals was slightly higher when the number of subjects who returned was considered irrespective of whether the subjects had been assessed at all other previous time intervals. The number of subjects who returned at 72 hours was noted as 57 for the all intervals assessment and 70 for the any intervals assessment which differs from the study report of 75 subjects. The study report noted that vital sign reporting did not lead to adverse event reporting, particularly for blood pressure which was linked to "procedure related stress" and "expected with this kind of examination." According to the study report, the highest number of out of range vital signs was reported for systolic blood pressure at 2 hours (N = 24) with slightly fewer out of range variations in SBP and DBP noted at 24 and 48 hours. This reviewer does not consider these were related to Dotarem injection.

For study DGD-44-050, vital signs were assessed at baseline then at 5 minutes, 15 minutes, and 24 hours post injection. According to the study report, mean changes in blood pressure and heart rate were minimal for the three time intervals. A few subjects had out of range changes at 24 hours consisting of decreased SBP and DBP with a few changes of either increased or decreased heart rate. Most pediatric subjects had within range vital signs at the 5 minute and 15 minute intervals with changes noted at 24 hours not assessed as clinically relevant.

For the remaining studies, when assessed vital signs were performed prior to injection and at various time points after injection. Respiration rate was occasionally measured. No vital sign safety signals were seen with the following general conclusions per study:

- DGD-30-44 ( CNS, N = 151): Few subjects with out of range data mainly for BP, variations not significant or clinically relevant and did not lead to AE reporting
- DGD-3-34 (CNS, N = 45): No clinically significant abnormalities in vital signs
- DGD-3-33 (CNS, N = 65): No clinically significant abnormalities in vital signs

- DGD-3-49 (Body, N = 120): 27 (22.5%) with DBP variation out of range for at least one point, not considered clinically significant or clinically relevant
- DGD-3-50 (Body, N = 110): 14 (12.8%) with at least one clinically relevant change in DBP, 14 (12.8%) with at least one clinically relevant change in SBP, 4 (3.7%) with at least one clinically relevant change in HR, 6 (5.5%) with at least one clinically relevant change in respiratory rate; investigator did not consider changes clinically significant and changes were not reported as AEs (? procedure related stress)
- DGD-44-44 (Renal safety, N = 142): No clinically significant vital sign outcomes or changes between groups
- DGD-44-042 (MRA, N = 92): ≤11% reported out of range variables, 1 event (increase SBP) reported as an AE
- DGD-44-046 (MRA, N = 33): 1 subject with BP and HR changes reported as AEs
- DGD-44-048 (MRA, N = 222): Only minimal vital sign changes
- DGD-44-049 (MRA, 212): Minimal vital sign changes, 1 subject with elevated BP not considered drug related
- DGD-44-045 (MRA, N = 189): Out of range vital sign changes for SBP (18 subjects, 9.8%), DBP (9 subjects, 4.9%), HR (3 subjects, 1.6%), changes not considered clinically significant and reported for both arms of the study
- DGD-44-52 (MRA, N = 20): 1 subject with out of range values for SBP not considered clinically abnormal

In summary, no relevant or consistent changes in blood pressure or heart rate were noted.

*Reviewer's Comments:*

- 1. Although the overall data provided for vital sign assessment does not suggest any safety signals or relevant changes, only 55% of subjects were monitored for vital sign changes.*
- 2. For the pivotal trial DGD-3-44, per protocol vital sign monitoring was performed for only 37.7% of subjects.*
- 3. This reviewer agrees with the applicant's comment that changes in vital signs are commonly reported in patients undergoing magnetic resonance examinations and notes are mostly related to anxiety or claustrophobic reactions*

#### 7.4.4 Electrocardiograms (ECGs)

In addition to the complete QTc study which was conducted, ECGs were performed in a subset of 91 adult subjects, (63 Dotarem, 28 Magnevist) and 12 pediatric Dotarem subjects in the -050 study. The evaluation for cardiac rhythm, (regular vs irregular), was based on information collected during the ECG asses at baseline and 30 minutes post injection and the differences were reported for RR, PR, QRS, QT, QRcB, and QTcF. A small and equivalent increase in QTcF and QTcB was seen for both Dotarem and Magnevist subjects and in pediatric subjects when comparing baseline to 30 minutes. 3/63 Dotarem subjects (4.8%) and 2/12 (16.7%) and no Magnevist subjects with a normal ECG at baseline developed an abnormal ECG. These consisted of 1 subject with flat T waves, 1 subject with inverted T waves, 1 subject with a sinus bradycardia and interventricular conduction defect, and 2 subjects with a slight increase in QTcB (where maximum was defined as 450 ms or >15 ms from baseline). No subjects had an abnormal QTcF (pre defined maximum of 450 ms).

The complete QTc study to assess cardiac safety is discussed in section 7.4.5 below.

#### 7.4.5 Special Safety Studies/Clinical Trial

Special Population safety studies included a phase 2 study to evaluate the effect of Dotarem on ECG parameters, a phase 3 study in subjects with chronic renal failure to evaluate the effect of Dotarem on image visualization and on various laboratory parameters, a phase 4 study to evaluate the effect of Dotarem on subjects with stable renal insufficiency, and a phase 1 PK study in 8 subjects with moderate (4 subjects) or severe (4 subjects) renal failure

The results of these studies are summarized in Table 28.

The applicant did not conduct any studies for age. However, in clinical studies of Dotarem, 900 subjects were 65 years of age and over, of which 312 patients were 75 years of age and over. No overall differences in safety were observed between these subjects and younger subjects. The applicant concluded that no dosage adjustment is necessary in this population.

Safety analysis gender study showed no effect on renal clearance with mean elimination half life of  $1.4 \pm 0.2$  hr in female subjects and  $2.0 \pm 0.7$  hr in male subjects and  $72.9\% \pm 17.0\%$  and  $85.4 \pm 9.7\%$  eliminated after 48 hours in female and male subjects.

Determination of urine zinc, copper, and iron was performed in a 24-hour urine collection as part of a PK study and showed an increase in zinc felt to relate to the study population which was young healthy males.

The applicant did not conduct any hepatic impairment studies however these would not be indicated due to the route of excretion (renal).

Study DGD-3-28 was a study in patients with chronic renal failure with comparison control to a population of healthy subjects. 12 patients were equally distributed in three groups of different stages of renal impairment or into a normal group as defined by serum creatinine clearance: (1) moderate impairment of creatinine clearance, (clearance <60 and >30 mL/min); (2) severe impairment (clearance <30 mL/min and > 10 mL/min) and; (3) normal renal function. Subjects received an 0.1 mmol/kg bw dose of Dotarem. Blood and urine PK parameters were evaluated before and after injection for 24 hours in the healthy subjects, for 48 hours in subjects with moderate impairment, and for 72 hours in subjects with severe impairment. The mean half life was 1.62 hours in normal subjects, 5.05 hours in subjects with moderate renal failure, and 13.9 hours in subjects with severe renal failure. Laboratory safety parameters were reported as satisfactory with no AEs reported. The overall conclusion was that decreased clearance of Dotarem was associated with increasing renal impairment but that no dosage adjustments were necessary for this group.

The primary objective of study DGD-48 was to calculate PK parameters of Dotarem after 0.1 mmol/kg injection in a group of healthy volunteers ages 18-45 and to calculate similar parameters in a second group that received a second injection of 0.2 mmol/kg after 20 minutes. Follow up was up to 48 hours. In the first group, there were differences in drug distribution attributed to higher body weight in men. Apart from this, the results of the study showed that exposure is dose proportional. 73-85% of the dose was recovered in urine over the 48 hour interval. Laboratory tests and vital signs were unremarkable. Four AEs were noted.

A thorough QT study was performed including PK. 40 subjects received an 0.1 mmol/kg dose of Dotarem followed by a second dose of 0.2 mmol/kg 20 minutes later. Eleven ECGs were recorded for each subject for each period. The central tendency analysis on absolute values and changes from baseline value of QT and/or QTc measured at numerous time points during the study showed no difference between active treatment and placebo. Results of the statistical analysis showed that Dotarem administration did not result in prolongation of QT or QTc intervals by more than 5 ms compared to placebo when analyzing maximal increases. Analysis of the AUC for both treatments confirmed this. Results of the analysis of outliers confirmed this. No QT or QTc value above 480 ms and no QT or QTc increase above 60 ms was observed after either treatment. No increase in QT or QTcF greater than 30 ms was observed after Dotarem administration. 6 patients had QT and QTc values greater than 450 ms, 3 under both treatments and 3 under Dotarem only. These occurred as isolated occurrences. 7 patients (4 under placebo, 3 under Dotarem) had QTcB increases above 30 ms. No clinically significant abnormalities were noted on other ECG parameters, (heart rate, Pr, QRS, T and U waves, 24 hour Holter recordings). 7 of the

40 patients reported adverse events that were mild to moderate in intensity, most frequently headache. There were no clinically significant abnormalities in the laboratory safety parameters or in vital signs. No definite cardiac signals were noted.

#### 7.4.6 Immunogenicity

2 subjects, (0.1%), in clinical trials experienced hypersensitivity reactions, one of which was assessed as an SAE. No subjects experienced anaphylaxis or an anaphylactoid reaction.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Drug related dose AEs were minimally more in the >0.1 mmol/kg dose group and were similar to comparators, (about 4%).

Overall, there was no apparent dose relationship for drug related AEs in the studies

#### 7.5.2 Time Dependency for Adverse Events

Most adverse events were mild or moderate in intensity, transient in nature, and occurred immediately or within 48 hours following Dotarem administration. A total of 32 AEs or 8.8% were considered severe with 4 AEs of headache, nausea in 2 subjects, and injection site pain consider related to Dotarem. The mean time to onset of AEs was 26 minutes. For related AEs the mean time to onset was 8 minutes and the mean duration time was 28 minutes. Most subjects received no treatment for their AEs and 72.5% recovered without treatment.

#### 7.5.3 Drug-Demographic Interactions

When drug AEs related for all subjects were stratified by baseline demographic characteristics and Dotarem dose and evaluated by the applicant the following conclusions were made and this reviewer agrees with the conclusions as follows:

- Of subjects who had related AEs, most (55.0%) were female, most (53.2%) were Caucasian.

- When stratified by gender, the incidence of all AES and treatment related AEs was similar in males and females (8.8% and 3.3% for males versus 10.0% and 4.8% for females).
- The mean age of subjects experiencing treatment related AEs was 49.9 years versus a mean age of 57.1 years for subjects who experienced non treatment related AEs.
- The incidence of treatment related adverse events was similar for all adult age groups (18 to <65 years, 65 to <75 years, ≥75 years).
- By age for the pediatric population, the incidence of AEs was greatest for the age group 6-<12 years, (10.3%) which was comparable to the overall incidence; there was a higher incidence in children in the under age 2 group not felt to be meaningful as this group consisted of only 7 subjects; incidence in the 2-<6 year old group was 6.1% and in the 12-<18 year group it was 4.7%.
- By ethnic group, AE incidence was higher in the Black population, (18.8%) compared to Caucasians (11.9%) and Asians (9.5%); for comparator drugs, the incidence in the Black population was only 14.3% and 0% in Asians, however it was increased to 20.2% in Caucasians
- When stratified by dose groups of <0.05 mmol/kg bw, 0.05-0.1 mmol/kg bw, and > 0.1 mmol/kg, the percent of subjects with treatment related AEs was 40.0%, 9.7%, and 8.6% respectively versus 2.5%, 15.2%, and 24.1% for comparator drugs respectively; when stratified for < 0.1 mmol/kg bw and both the 0.2 mmol/kg bw and 0.3 mmol/kg bw doses, approximately 10% of subjects experienced AEs at the lower doses and 20-25% of subjects experienced AEs at the higher doses
- The age and female percent are reflective of the study populations although the percentage of Caucasians is significantly less than the percentage enrolled in clinical trials, (74.4%).
- The overall subject numbers at lower doses were insufficient for meaningful conclusions; the AE rate between 0.05-0.1 mmol/kg bw as well as at a dose of 0.09-0.11 mmol/kg was approximately 10%, somewhat higher for comparators, and at the 0.2 and 0.3 mmol/kg doses was also approximately 10%

**This reviewer agrees that the incidence of drug related AEs by gender, age, and dose group were comparable within the subgroups with no specific gender, age, or race related trends were noted.**

#### 7.5.4 Drug-Disease Interactions

Dotarem must be used with caution in patients with chronic renal impairment or acute renal injury. Gadolinium is thought to act as a “trigger” for nephrogenic systemic fibrosis which potentially may be caused by any gadolinium-based contrast material.

### 7.5.5 Drug-Drug Interactions

Dotarem is an extracellular gadolinium-based contrast agent which is rapidly distributed in the extracellular space after administration. It is not metabolized and is eliminated by the kidneys via glomerular filtration. The extrarenal (biliary) elimination is negligible.

There is no potential risk for drug-drug or drug-food interactions. No relevant drug-drug or drug-food interactions have been identified in clinical trials or in post marketing experience.

No drug interaction studies were performed however none were observed in clinical trials. As Dotarem is not metabolized, a metabolic drug interaction with a co-administered drug is unlikely.

## 7.6 Additional Safety Evaluations

Non clinical P/T studies showed no immediate hypersensitivity reactions. These reactions are known to occur in all agents in this class. In clinical trials, the AE of hypersensitivity reaction was reported 2, (0.1%) subjects. The AE rate comparing subjects in clinical trials with and without a history of allergy was similar.

### 7.6.1 Human Carcinogenicity

No carcinogenicity study was performed, (none required). Genotoxicity studies and mutagenicity studies were negative.

### 7.6.2 Human Reproduction and Pregnancy Data

There is no available information on drug exposure in pregnant women for this drug. Gadolinium based contrast agents are known to cross the placenta and thus to result in fetal exposure. Non-clinical studies for Dotarem showed that minimal amounts of were transferred transplacentally to rats with an 0.5 hr. maximum time. PK studies showed excretion in goat milk. It is not known whether Dotarem is excreted in human milk.

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

area) and in rabbits at 7 mmol/kg/day (23 times the human dose based on body surface area).

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No studies were performed in juvenile animals to support the use of Dotarem in children below one year of age.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

This is an imaging drug with no drug abuse potential.

## 7.7 Additional Submissions / Safety Issues

### Safety in Subjects With Renal Failure:

The applicant conducted 3 clinical trials in subjects with renal impairment, with comprehensive assessment of biochemical and hematologic parameters performed for all subjects. In studies where control groups were studied, there were no significant differences in laboratory parameters post Dotarem with either no significant clinical abnormalities, no clinically significant difference between control and Dotarem groups, or clinically significant but chronically typical abnormalities. In all clinical trials, 1 subject experienced an AE of renal failure. There was no difference in the incidence of AEs for subjects with renal disease compared with the incidence of AEs in the total subject population without renal disease.

### Nephrogenic Systemic Fibrosis (NSF)

The Applicant confirmed the administration of Dotarem in 16 out of 38 cases where Nephrogenic Systemic Fibrosis was coded as the adverse reaction. Of these, there were 5 confirmed or very likely cases of NSF using the Girardi score and 11 unconfirmed or doubtful cases based on missing information which did not allow the Girardi score to be applied and/or the differential diagnoses cannot be ruled out. All 5 of the confirmed or likely cases were multiple agent cases. 2 of the unconfirmed or doubtful cases were single agent cases. Based on this, the applicant has reported 0 cases of nephrogenic systemic fibrosis, (NSF) as of 9-20-12 submitted to the US IND 65,041. The number of exposures reported as of this same date is approximately 30 million.

### Safety in the Pediatric Population

Three dedicated pediatric trials were conducted in the 1.2 month-18 years population enrolling 99 subjects (92 subjects under age 17). There were an additional 38 subjects ages 2-18 enrolled in the -050 trial and 4 subjects, (ages 12 years, 16 years and 2 subjects age 17 years), enrolled in other CNS trials with 141 as the total number of children in the safety database when the 17 year old population is included. By age distribution, there were 7 subjects ages 1-24 months, 33 subjects ages 2-6 years, 58 subjects ages 6-12 years, and 43 subjects ages 12-18 years.

As already noted, no pediatric PK studies and no dose ranging studies were conducted. Safety evaluation in the three supportive pediatric trials consisted of AE evaluation for all subjects and laboratory monitoring of 20 subjects in the phase 2 DGD-15 trial.

The focus of this discussion is the population under age 2 years based on the proposed indication to include this age group.

7 subjects under age 2 were studied in the 3 clinical trials of which two were monitored by laboratory parameters. Dotarem dose was similar for the 3 trials, 0.1 mmol/kg. Dotarem was administered to all 3 subjects under age 2 in the DGD-3-15 trial at a flow rate of 3 mL/minute and was diluted in saline with a flow rate range of 2-5 mL/min used for all subjects. Dotarem was administered to the two subjects in the DGD-3-16 trial at a flow rate of 3 mL/minute also, but not diluted in saline with a flow rate range of 1-3 mL/min for all subjects. Dotarem was administered to 2 subjects under age 2 in the DGD-2-29 study, by bolus injection, rate not specified.

When laboratory data for all 20 subjects in the DGD-3-15 study was assessed, it was noted that 15 of the 20 subjects had at least one missing laboratory parameter. One subject in this study, age 1.2 months, had marked fluctuations in laboratory values which were attributed to a chronic process. There was one AE noted in the population, a 5 year old child who vomitted 30 minutes after Dotarem administration. Subjects in the three studies were assessed for AEs up to 24 hours for the DGD-15 study but only for 20 minutes post injection for DGD-3-16 and 45 minutes post injection for DGD-3-29.

Guerbet conducted 5 post marking studies which include children under age 2 years. A sixth study is ongoing. There is no way to independently verify the data in these studies. Data presented by the applicant consists of study reports, journal articles and abstracts. Safety monitoring for all these studies was for adverse events. Summaries of these studies follow from the NDA submission references:

- Briand Y. et al, "Efficacy and Safety of the Macrocyclic Complex Gd-DOTA in Children: Results of a Multi-Centre Study", Friday Session 10 R12 European Society of Pediatric Radiology, 1992: Dotarem dose for all children studied ranged from 0.10 to 0.78 mL/kg, (mmol/kg not given), 26 subjects age 2 or below showed improved diagnostic evaluation and no AEs were reported

- Emond S. and Brunelle, Gd-DOTA administration at MRI in children younger than 18 months of age: immediate adverse reactions. *Pediatric Radiology* 2011; 41: 1401-1406: 104 children received a single injection of 0.1 mmol/kg Dotarem followed by a saline flush of the same volume as the Dotarem, no adverse events were noted
- Isiguchi T. and Takahashi S. Safety of Gadoterate Meglumine (Gd-DOTA) as a Contrast Agent for Magnetic Resonance Imaging Results of a Post-Marketing Surveillance Study in Japan. *Drugs R D* 2010; 10 (3): 133-145: 41 children under age 15 (number under age 2 not specified) were injected with an average dose of 0.1 mmol/kg with 2 children receiving more (1.7 and 1.9 times the recommended dose), no adverse events reported
- Maurer, M. German PMS Dotarem. 2004: observational study which included 10 children under age 2 assessed for adverse events (none noted), mean dose was slightly greater than 0.1 mmol/kg
- Neiss AC et al. Efficacite et tolerance du DOTA-Gd lors d'une enquete multicentrique europeenne. *Revue d'Imagerie Medicale* 1991 3: 383-87: 305 children under age 18 received Dotarem as 0.075-0.125 mmol/kg for 77.4% of children, study supportive of safety profile

According to post marketing pharmacovigilance data, 8 patients  $\leq$  2 years (0.5% of population) with 10 ADRs have been reported, 2 considered as serious and unlisted, 6 as non serious listed and unlisted. All subjects recovered. 4/10 events are listed as injury, poisoning, and procedures noted 3 to be med errors of overdose or accidental overdose and 3/10 for general disorders and administration site disorders with 2 as extravasation. This reviewer noted that this section is unclear about the breakdown of the terminology and events. There was one SAE of heart rate increase and then a decrease that was not associated with any medication errors.

*Reviewer's Comments:*

- 1. Clinical trial data does not support approval in children under age 2 years.*
- 2. No PK studies were conducted in any pediatric age group.*
- 3. The applicant has proposed a juvenile pharm/tox study but no similar studies were submitted to the NDA.*
- 4. Clinical trial monitoring was inadequate to confirm safety with a total of 7 subjects included in the trials of which only 2 were monitored with laboratory parameters. Vital signs were not monitored. AE event monitoring was variable—from 15 minutes to 24 hours—inconsistent, and not as “controlled” as current monitoring, for example injection site reactions were not evaluated as AEs.*

5. *In clinical trials, Dotarem doses and administration rates were not strictly controlled, were variable for the 3 pediatric studies, and differ from the label in the NDA.*

6. *There is no way to independently verify the data in the post marketing reports. On review of the literature submitted to the NDA, slightly variable doses and administration rates are noted and for all studies and only AEs were monitored.*

## 6 Postmarket Experience

The source of review for postmarketing were the safety updates contained in the NDA submission, (3-8-89 birthdate to March 31, 2012), Cumulative Safety Data, and the 120 day safety update submitted to the NDA covering the time frame from 4-1-12 through 10-31-12.

The number of exposures to Dotarem reported as of 9-20-12 is 30 million.

Post marketing surveillance since initial launch of Dotarem in the EU in March 1989 forms the overall basis of safety data from spontaneous reports. More than 30 million prescriptions have been dispensed since that time. Cumulative data analysis using MedDRA SMQs (standardized MedDRA Queries) and SOC's (System Organ Class) for higher medical relevance for the period from initial launch in March 1989 through 31 March 2012, yields a total of 1791 post marketing individual cases corresponding to 3947 suspected adverse reactions reported by health care professionals, health authorities, literature, and patients to Guerbet. The adverse reaction rate is estimated to be (b) (4). The rate of serious adverse reactions is estimated to be (b) (4). The incidence of anaphylactoid reaction is (b) (4). The incidence of death (24 deaths) is 0.08/100,000.

ADRs were assessed according to the French imputability method, (actualization of the method used in France), using the following reference: Begaud B, et.al. Unexpected or toxic reaction assessment (imputation). Actualization of the method used in France (English translation). Therapie 1985; 40: 115-118.

Using MeDRA version 14.1, the most frequently affected body systems were as follows:

- Skin and subcutaneous disorders (26.9%) with 1061 adverse drug reactions (ADR) noted in 770 patients. Urticaria was the most frequently reported reaction, accounted for 311 ADRs with most of the remaining cases non-serious rashes.
- Gastrointestinal disorders (18.4%) with 726 ADRs in 563 patients. Nausea, the most frequently reported reaction, accounted for 358 ADRs with vomiting accounting for 252 ADRs. Most of these reactions were not serious.
- Respiratory, thoracic, and mediastinal disorders (13.7%) with 541 ADRs in 373 patients. Sneezing, the most frequently reported reaction, accounted for 136

ADRs with dyspnea accounting also for 136 ADRs. These reactions were occurred in the context of hypersensitivity reactions.

- Nervous system disorders (7.0%) with 278 ADRs in 235 patients. Headache, the most frequently reported reaction, accounted for 44 ADRs with paresthesias accounting for 38 ADRs and dizziness for 33 ADRs. Most of these reactions were not serious
- Immune disorders (6.2%) with 246 ADRs in 166 patients. The most frequently reported ADRs were hypersensitivity/anaphylactoid reactions, consisting primarily of cutaneous, respiratory, and cardiovascular symptoms. This set of ADRs occurs in association with all GBCAs including instances of life threatening or fatal shock.

Table 34 summarizes the ADRs and SAEs by System Organ Class classification as discussed above at the pre-NDA meeting in June, 2012.

**Table 34 Post Marketing Adverse Drug Reactions and Serious Adverse Reactions by System Organ Class**

<b>System Organ Class (SOC)</b>	<b>All Adverse Reactions</b>	<b>Serious Adverse Reactions</b>
Blood disorders	2 (0.05%)	1 (0.03%)
Cardiac disorders	90 (2.3%)	68 (1.7%)
Ear and labyrinth disorders	23 (0.6%)	11 (0.3%)
Eye disorders	123 (3.1%)	49 (1.2%)
Gastrointestinal disorders	726 (18%)	186 (4.7%)
General disorders and administration site condition	409 (10.4%)	181 (4.6%)
Hepatobiliary disorders	4 (0.1%)	4 (0.1%)
Immune system disorders	246 (6.2%)	152 (3.8%)
Infections and infestations	22 (0.6%)	13 (0.3%)
Injury, poisoning, and procedural complications	134 (3.4%)	10 (0.3%)
Investigations	38 (1.0%)	35 (0.9%)
Metabolism and nutrition disorders	7 (0.2%)	3 (0.1%)
Musculoskeletal and connective tissue disorders	35 (0.9%)	15 (0.4%)
Nervous system disorders	278 (7.0%)	165(4.2%)
Pregnancy, puerperium, and perinatal conditions	12 (0.3%)	7 (0.2%)
Psychiatric disorders	24 (0.6%)	16 (0.4%)
Renal and urinary disorders	23 (0.6%)	19 (0.5%)
Reproductive system and	1 (0.02%)	1 (0.02%)

breast disorders		
Respiratory, thoracic, and mediastinal disorders	541 (13.7%)	295 (7.5%)
Skin and subcutaneous tissue disorders	1058 (26.8%)	409 (10.4%)
Surgical and medical procedures	7 (0.2%)	3 (0.1%)
Vascular disorders	141 (3.6%)	97 (2.5%)

26 cases of death have been reported to the post marketing safety data base with ages ranging from 3 to 84 years. 21 of these were males. According to the applicant, all cases had confounding factors such as cardiovascular disease, renal disease, and cancer. Death was reported ranging from the same day up to 36 months after Dotarem administration. The causes of death were reported as follows: anaphylaxis/anaphylactic shock (N = 5), cardiac arrest (N = 9), multiorgan failure (N = 3), sepsis (N = 2), cancer (N = 2), cerebroembolism (N = 1), and unknown (N = 3; other GBCAs were administered). In 14 cases death was most likely related to anaphylaxis or cardio pulmonary arrest possibly related to anaphylaxis.

Guerbet conducted a large post marketing observational study to evaluate the risk/benefit of Dotarem. The study included 104,033 patients, 44.9% males and 54.0% females ranging in age between 5 weeks and 97 years, with 23.1% of the population having risk factors, most commonly allergies (12.3%) and hypertension (6.1%). 0.7% (691 patients) of the study population received premedication prior to Dotarem administration. MRI examinations were most frequently used for neurological examinations (49.1%) with 36.1% of exams for CNS evaluation, with bone and joint studies in in 32.2%, evaluation of internal organs in 12.7%, MRA in 2.4%, and other exams in 5.1%. 90% of all patients received 10-20 mL of Dotarem with a mean volume of 16.1mL and a range of 0.6 to 38 mL. Adverse events occurred in a total of 328 patients (0.3%), most commonly nausea which occurred in 174 patients. 31 serious adverse events were reported in 11 (0.01%) patients with relationship to Dotarem possible for 7 of these. The sponsor states that this study enabled diagnosis for 99.7% of the patients and that image quality was very good or good in 97.2% of patients. According to the sponsor, the low rate of adverse events and serious adverse events supports the safety of Dotarem.

The conclusion of this reviewer is that the overall postmarketing safety profile is acceptable and that the adverse events are common to all GBCAs..

## **9 Appendices**

### **9.1 Literature Review/References**

The 5 post marketing literature references provided by the applicant as support for the CNS indication in children under age 2 were reviewed and cited in the section above. No additional literature review or references were used for this NDA review.

### **9.2 Labeling Recommendations**

Pending.

### **9.3 Advisory Committee Meeting**

An Advisory Committee meeting has been scheduled for 2-14-13.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BARBARA A STINSON  
02/09/2013

ALEXANDER GOROVETS  
02/10/2013

The clinical Team Leader has examined this document and indicates a concurrence with its general content. This document remains as filed by the primary reviewer and has not been further edited for grammar, syntax, typographical errors or formatting.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number:** 204,781      **Applicant:** Guerbet LLC      **Stamp Date:** 9-20-12

**Drug Name:** Dotarem® Injection      **NDA/BLA Type:** Original  
NDA, Priority Review

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			Organization by module 5 individual studies and study summaries is generally acceptable
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			Navigation through the submission, to include the clinical section, is acceptable
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			Navigation of older documents is difficult but can be done; pages “jump” rather than scroll smoothly
5.	Are all documents submitted in English or are English translations provided when necessary?		(x)		Portions of studies examined are not translated; at least one reference is not translated and has no abstract (see comments below)
6.	Is the clinical section legible so that substantive review can begin?	x			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			ISS and ISE present but not well distinguished from remainder of module 5 contents; contents are in 5.3.5.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			x	505(b)(1)

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>DOSE</b>					
13.	<p>If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i>, appropriately designed dose-ranging studies)?</p> <p>Study Number: DGD-3-48</p> <p>Study Title: Pharmacokinetic Study of GD-DOTA After 0.1 mmol/kg and 0.1 + 0.2 mmol/kg Intravenous Injection in Healthy Male and Female Volunteers</p> <p>Sample Size: 16 subjects/group</p> <p>Arms: 2</p> <p>Location in submission: 5.3.3.1</p>			x	<p>PK study for safety and tolerability in adults only; no CNS dose ranging studies for efficacy. Clinical Overview section 2.5.1.4.2 states that Dotarem dose was based on 0.1 mmol/kg which was the already recognized dose in the literature as being effective for gadolinium complexes and as was already used for Magnevist whose general PK and effects on MRI signals were supposedly identical to Dotarem</p>
<b>EFFICACY</b>					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1 Safety and Efficacy Evaluation of Dotarem® in Magnetic Resonance Imaging (MRI) in Patients with Central Nervous System (CNS) Lesions (Protocol No. DGD-44-050, SENTIO Study)</p> <p>Indication: Dotarem is a gadolinium based contrast agent for intravenous use with magnetic resonance imaging (MRI) in the brain (intracranial) spine and associated tissues in adults and pediatric patients (b) (4) to detect and visualize areas with disruption of the blood-brain barrier and/or abnormal vascularity</p> <p>Pivotal Study #2 Blinded centralized re-reading of a Phase IIIb study (original protocol DGD-3-44 Evaluation of MRI with Dotarem in the diagnosis or follow-up assessment of cerebral or spinal tumors)</p> <p>Indication: Same as above</p> <p>Guerbet conducted additional clinical studies for the CNS indication in the pediatric population.</p> <p>Study DGD-44-050 enrolled 38 children from 2 to 17 years of age for safety and efficacy evaluation of Dotarem in MRI in patients with CNS lesions.</p> <p>3 additional open-label, single group clinical studies enrolled children ages 15 days through 17 years, (DGD-3-15, DGD-3-16, and DGD-3-29), who received Dotarem for MRI procedures for the diagnosis and detection of various suspected cerebral lesions, the detection of local recurrence</p>	x			<p>Pivotal study #1 as an SPA is acceptable; pivotal study #2 (original study) limited safety, limited population evaluated and other factors that will be review issues; pediatric studies did not adequately evaluate safety and enrolled insufficient numbers in the under age 2 population, both of which will be review issues</p>

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	of disease, the exploration of the anatomical structure of lesions, or as a routine procedure for therapeutic follow-up				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			Study DGD-44-050 conducted under SPA; Study DGD-44-051, blinded centralized re-read of a phase 3 study
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Population for re-read study limited inclusion criteria, over 97% Caucasian and all but 1 site was in France, all review issues; for the SPA study, over 87% Caucasian, limited diversity, but probably acceptable, also review issues
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			Safety data may be inadequate (review issue) but appears to be acceptable in manner presented
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	x			Study DGD-44-039 in module 5.3.4.2 titled "Evaluation of Electrocardiographic Safety of Dotarem®"
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			x	Not a chronically administered drug
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	x			Stated directory and terminology used

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Safety summary from Birthdate through 3-31-12 as well as individual PSURs are submitted
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			Applicant did not discuss pediatric studies and clinical workup with Division, review issue deficiencies
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			Datasets verification is pending statistical reviewer's comments
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	x			

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## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?\_Yes\_\_\_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. Although no Refuse To File comments are being contemplated the following additional comments have been made during the filing review:

- Although the application has been ultimately found to be fileable we note that some reference translations are missing. These will be requested as needed.
- We also note that the applicant has not conducted any dose ranging studies. It is not clear at this time if these were “needed” as per the filing form above. This will be a review issue as discussed with our Clinical Pharmacology colleagues. We also note that there have been no PK studies conducted in pediatric population in general and specifically in pediatric patients under age 2.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- No dose ranging studies were conducted
- No PK studies in pediatric population under age 2; no PK studies in pediatric population ages 2-17 years
- Not all studies and references are translated
- No safety studies conducted to assess placebo versus study drug
- Pivotal studies population demographics, over 97% Caucasian for one study and over 87% Caucasian for second study; may not represent proposed population
- Ethnicity studied limited for second pivotal trial with 8/9 sites located in France
- Limitations of enrollment criteria for second trial (tumoral disease only; brain only)
- Limitations of safety monitoring; about 25% of subjects in clinical trials received extensive safety monitoring, 75% monitored for adverse events with some monitored also for vital signs and subjective visual analogue scale
- Normal range missing for laboratory parameters for several studies
- In one of the two pivotal studies safety assessments were limited to only vital signs and adverse events

Barbara A. Stinson, DO  
 \_\_\_\_\_  
 Reviewing Medical Officer

11-15-12  
 \_\_\_\_\_  
 Date

\_\_\_\_\_  
 Clinical Team Leader

\_\_\_\_\_  
 Date

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BARBARA A STINSON  
11/18/2012

ALEXANDER GOROVETS  
11/18/2012