Advisory Committee Briefing Document

Dotarem® (gadoterate meglumine) Injection

Medical Imaging Drugs Advisory Committee (MIDAC)

14 February 2013

Guerbet LLC

NDA 204-781

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE.

1 EXECUTIVE SUMMARY

This document is prepared by Guerbet LLC for the Medical Imaging Drugs Advisory Committee Meeting to be held on February 14, 2013. It provides data supporting the efficacy and safety of Dotarem use in adult and pediatric patients (from neonates to 17 years of age) for MRI of the CNS.

1.1 Development History

The key features of Dotarem development are the following:

- Dotarem has been chemically designed to be both a macrocyclic and ionic Gadolinium-based contrast agent (GBCA) to ensure the highest stability among GBCAs.
- Dotarem was first approved in 1989 (France). Contrast-enhanced magnetic resonance imaging (CE-MRI) of the Central Nervous System (CNS) was the first approved indication and is the most widely used application for Dotarem.
- Dotarem is marketed in vials and pre-filled syringes. To date, approvals have been obtained in more than 70 countries worldwide. In most countries, Dotarem is approved for use in adults and pediatric patients, including neonates and infants. The list of approvals and indications approved per countries is provided in Appendix 1.
- Recommended dose of Dotarem is 0.1 mmol/kg body weight (BW), with higher doses up to 0.3 mmol/kg BW approved in many countries for some specific uses.
- Efficacy and safety of Dotarem have been well characterized in a total of 49 clinical studies involving 2813 patients exposed to Dotarem, including 141 pediatric patients between 0 to 17 years of age.
- Safety profile is supported by post-marketing experience from approximately 30 million doses administered over 2 decades of approved use worldwide.

The overall development program completed by Guerbet for this NDA supports the conclusion that Dotarem is both safe and effective to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity in the brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonates to 17 years of age).

1.2 Proposed Indication and Usage

A New Drug Application for Dotarem is undergoing review by the Medical Imaging Drugs Division of the FDA and has been assigned a “Priority Review” classification, as the product meets an unmet medical need for use in pediatric population less than 2 years of age.

The proposed indication is:

"Dotarem is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in the brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonates to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity."

The recommended dose of Dotarem in adults and pediatric population (neonates to 17 years of age) is 0.1 mmol/kg calculated by body weight (BW).

1.3 Medical Need for an Approved Indication in Pediatric Population Less Than 2 Years of Age

There is an unmet medical need for an approved MRI contrast agents use in pediatric patients less than 2 years of age in the US.

In the recent years, MRI techniques are gaining popularity in pediatric imaging mainly because they provide.

- High soft tissue definition and discrimination in the CNS, such as detection of early tumors, vascular malformations, detailed grey matter/white matter distinction; heightened sensitivity for detection of cerebral and spinal anomalies.
- Desirable alternative to heightened sensitivity to exposing young children, especially the most vulnerable less than 2 years of age group, to the risks of ionizing radiation from CT (Pearce *et al.*, 2012).
- Smaller volumes of contrast agent to be administered to these small children compared with the typical volumes of iodinated contrast agent used with CT.
- Alternative method for cross-sectional imaging of the brain and spine.

There is currently no GBCA approved in the US for use in pediatric population less than 2 years of age. The current practice for diagnostic or disease management in this population is off-label use of the currently approved GBCAs in the US. Various GBCA differ in chemical structure, stability and level of Gd release in vivo as evidenced by the recent observation of nephrogenic systemic fibrosis (NSF) in other patient populations that is felt to be related to release of free Gd.

This difference in risk level has been recognized by the FDA which has resulted in issuance of a Medical Drug Alert Directive in 2010 contraindicating the use of higher risk GBCAs in patient populations with renal compromise (GFR <30). However, the use of higher risk GBCAs for pediatric population less than 2 years of age is still common today. For example, in a web-based survey concerning contrast media usage in children including responses from 42 Chairs of Radiology in children's hospitals in North America predominantly in the US (Trout, et al., 2011), the most common GBCA used in children is Magnevist (81% of respondents) followed by MultiHance (38% of respondents). Omniscan or OptiMARK is

used by 12% of respondents. Furthermore, regarding GBCA dosing, 43% of the respondents indicated that they do not strictly follow the FDA's black box warning for the use of GBCA in children with renal insufficiency. This practice may be especially inappropriate in this vulnerable age group and especially in children with chronic diseases and tumors which may require observation and monitoring with serial Gd-enhanced MRI scans over a lifetime.

Dotarem has been approved for MRI use in the CNS in all pediatric patients, including those less than 2 years of age, in most countries outside US where it is approved in adults. The safety and efficacy of Dotarem in the CNS has been well characterized in post-marketing use of over 51,000 doses administered in pediatric patients less than 2 years of age. Dotarem has the highest thermodynamic and kinetic stability among all GBCAs, currently in clinical use and approved for use in more than 70 countries.

Approval of Dotarem for use in children less than 2 years of age will help to guide imaging physicians in the US to use a GBCA that is efficacious, stable and has a demonstrated safety record.

1.4 Non-Clinical Development

Based on the results of the non-clinical studies, Dotarem is not expected to induce any severe or irreversible adverse effects in humans after an IV bolus injection at the recommended dose (0.1 mmol/kg). The following observations and conclusions were made from non-clinical studies after IV injection:

- Dotarem is rapidly distributed in the blood volume and extracellular fluid. It is not bound to plasma proteins and is rapidly excreted unchanged in urine.
- Dotarem did not cause adverse effects on any main physiological functions when administered at the clinical dose level. Only minor and transient effects were observed at dose levels that were much higher than the recommended human dose (see Section 6.3.1).
- No safety concerns arose from single-dose and repeat-dose toxicology studies.
- Dotarem is not mutagenic.
- No effect on mating performance and fertility (rats) and no teratogenicity or embryotoxicity (rats and rabbits) were observed after repeated injections of several times the recommended human dose.
- Local tolerance of Dotarem was found to be satisfactory, even in case of misadministration outside the vein (extravasation).
- A very low risk of NSF is anticipated for Dotarem, based on its high kinetic and thermodynamic stability and the lack of free Gd release observed in non-clinical studies. This is fully consistent with clinical studies and post-marketing experience, as no single-agent cases of NSF has been reported in humans with Dotarem after approximately 30 million exposures since initial approval in 1989.

1.5 Clinical Pharmacology

Notable information about the clinical pharmacology of Dotarem is:

- After IV injection, Dotarem is rapidly distributed in blood and extracellular fluid. It is rapidly excreted in urine in subjects with normal renal function. Urinary elimination is delayed with renal impairment.
- No dose adjustment is required for any patient population.
- Dotarem does not induce any modification of ECGs and does not induce QT/QTc interval prolongation.

1.6 Efficacy

The efficacy of Dotarem in MRI of the CNS has been demonstrated in 2 adequate and well-controlled pivotal Phase III studies. All defined primary and key secondary efficacy analyses were positive and support the efficacy of Dotarem at a standard dose of 0.1 mmol/kg BW.

Statistically significant superiority in lesion visualization on "Paired" images (unenhanced plus Dotarem-enhanced MRI) over "Pre" images (unenhanced MRI) was demonstrated across all readers and in both studies, for all three co-primary endpoints:

- Lesion border delineation
- Lesion internal morphology
- Lesion contrast enhancement

In addition to these 2 pivotal studies, 21 supportive clinical studies concurred with the efficacy of Dotarem-enhanced MRI. Supportive studies showed that Dotarem-enhanced images were superior to unenhanced images with regard to clinically relevant imaging parameters.

Regarding specifically the pediatric population from 0 to 17 years of age, efficacy of Dotarem in the CNS indication was assessed in pivotal study DGD-44-050 and in 3 open-label, single-group, non-randomized studies (DGD-3-15, DGD-3-16 and DGD-3-29). Efficacy results obtained in the pediatric population were consistent with those obtained in the adult population. Dotarem-enhanced MRI produced significant improvement in the ability to detect and visualize CNS lesions and the overall image quality.

Dotarem, administered at the recommended dose of 0.1 mmol/kg BW, improves diagnostic capabilities over unenhanced MRI alone for detection and visualization of CNS lesions in both adult and pediatric populations.

1.7 Safety

Accumulated safety data of Dotarem are summarized below:

- The clinical safety profile of Dotarem has been well characterized during a large clinical development program (49 clinical studies including 2813 adults and pediatric patients exposed to Dotarem).
- The most frequently reported related adverse events (AE) were nausea, headache and injection site pain.
- 29 serious adverse events (SAEs) (including fatalities) were observed in 23 (0.8%) patients treated with Dotarem. Among SAEs in Dotarem-treated patients, 2 were considered to be possibly related to Dotarem administration (moderate hypersensitivity and mild increase in serum creatinine) and none of them were fatal.
- Six post-marketing observational studies with more than 137,000 patients provide reassuring additional safety data for both adult and pediatric populations.
- Accumulated post-marketing safety data, based on approximately 30 million doses, demonstrated a well-characterized safety profile consistent with the AEs observed in clinical studies. Most reactions were reported in the system organ classes of Skin and subcutaneous tissue disorders (26.9%), Gastrointestinal disorders (18.4%) and Respiratory, thoracic and mediastinal disorders (13.7%).
- Based on the clinical studies and supported by the results of the post-marketing observational studies, Dotarem was well tolerated in pediatric patients, including those less than 2 years of age. Accumulated safety data in children do not differ from what is currently known in the adult population.
- No cases of NSF or NSF-like symptoms have been observed in clinical studies. No single-agent/unconfounded cases of NSF were reported for Dotarem in the post-marketing experience. The assessment was based on the criteria of Girardi (Girardi et al., 2011).

1.8 Efficacy and Safety in Pediatric Population Less Than 2 Years of Age

During the Dotarem pre-NDA meeting held on June 12, 2012, it was established between the FDA and Guerbet to include the current available clinical and post-marketing data to support the proposed CNS indication for the pediatric population less than 2 years of age.

The 3 clinical studies and the 6 prospective post-marketing observational studies that included a total of 241 pediatric patients less than 2 years of age provided a good level of efficacy and safety, consistent with those found for adult patients and pediatric patients older than 2 years of age.

Overall, in terms of safety:

- In clinical studies, there were no related AEs as reported by investigators. However, one AE was temporarily associated to the administration of Dotarem (mild vomiting occurred in one female patient who did not required treatment).

- In post marketing observational studies, no AE were reported by investigators.
- In post marketing setting, 8 pediatric patients have reported 10 adverse drug reactions (ADRs), including one serious ADR. The reactions observed in pediatric patients less than 2 years of age were mostly due to medication errors (such as overdose) or extravasation. No anaphylactic reactions, SAE or death have been reported.
- No NSF events were described in this population in clinical studies, post-marketing observational studies and post marketing experience.

Overall, based on clinical studies (N=7 patients), post marketing observational studies (N=234 patients) and post marketing experience (N>51,000 patients), the safety and efficacy data of Dotarem provide a good level of confidence regarding the benefit risk ratio for the pediatric population less than 2 years of age and support the proposed indication in this patient population.

1.9 Benefit/Risk Profile and Conclusions

This application focuses on the efficacy and safety of 0.1 mmol/kg BW of Dotarem for CE-MRI of the CNS. The overall safety profile of Dotarem has been systematically characterized in clinical programs in 2813 patients exposed to Dotarem, in post-marketing observational program in more than 137,000 patients and in post-marketing experience of approximately 30 million doses administered in over 20 years of use. Since 2007, after the first NSF labeling changes were introduced outside the US, worldwide usage of Dotarem, including for pediatric patients less than 2 years of age, has increased significantly, confirming and strengthening the positive benefit/risk ratio. Numerous regulations worldwide and radiological societies such as the American College of Radiology (ACR) consider Dotarem as a GBCA with a low NSF risk (ACR Manual on Contrast Agents, 2010).

The potential risk for NSF after receiving Dotarem appears to be very low resulting in a positive benefit/risk assessment for patients with severe renal impairment. Dotarem will be particularly beneficial to US patients with severe renal impairment or pediatric patients less than 2 years of age.

Accumulated safety data in pediatric patients are in line with what is currently known in the adult population. Approval of Dotarem for pediatric population use has been granted in European countries, with no increase in reported adverse reactions. New techniques utilizing GBCAs are improving diagnosis. Continued development of sophisticated imaging sequences will provide faster and better examinations in the pediatric patient population. In the US, gadolinium contrast agents are currently approved for IV use in the patients over 2 years of age, but off-label applications are frequently utilized in pediatric patients less than 2 years of age. Dotarem provides a safe and effective MRI contrast agent for pediatric patients less than 2 years of age.

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List of Abbreviations

Acronym/Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
BBB	Blood brain barrier
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BW	Body weight
C	Comparative
CE-MRI	Contrast-enhanced magnetic resonance imaging
CI	Confidence interval
Clr	Renal clearance
Clt	Total clearance
C_{max}	Maximum concentration
CNS	Central nervous system
CT	Computerized tomography
DB	Double blind
DOTA	Tetraazacyclododecanetetraacetic acid
DTPA	Diethylenetriaminepentacetate
ECG	Electrocardiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLAIR	Fluid attenuated inversion recovery
GBCA	Gadolinium-based contrast agents
Gd	Gadolinium
HR	Heart rate
HPLC	High performance liquid chromatography
ICP-MS	Inductively coupled plasma mass spectrometry
IND	Investigational New Drug (application)
IV	Intravenous
K_{cond}	Conditional stability constant at physiological pH
K_{therm}	Thermodynamic stability constant
M	Multicenter
Max	Maximum value
Min	Minimum value
mOsm	Milliosmols
mPa.s	MilliPascal-second
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
ND	Not done
NR	Not randomized
NSF	Nephrogenic Systemic Fibrosis
O	Open label

Acronym/Abbreviation	Definition
"Paired"	Unenhanced images and enhanced images (includes all of the unenhanced sequences as well as the contrast-enhanced T1-weighted sequence)
PG	Parallel groups
"Pre"	Unenhanced images (T1-weighted, T2-weighted and FLAIR)
"Post"	Contrast-enhanced images (T1-weighted)
QTc	Corrected QT
R	Randomized
r1	Longitudinal relaxivity
r2	Transverse relaxivity
RMP	Risk Management Plan
RR	Respiratory rate
S	Single center
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SPA	Special Protocol Assessment
T1	Longitudinal relaxation time
T2	Transverse relaxation time
$T_{1/2}$	Half-life
TO	Before injection
US	United States of America
VAS	Visual Analog Scale

3 INTRODUCTION

3.1 Contrast-Enhanced Magnetic Resonance Imaging (CE-MRI)

MRI is a key technique for CNS imaging in adults and children. Based on magnetic and radiofrequency fields, MRI allows anatomic images in multiple planes and excellent soft tissue contrast resolution without ionizing radiation exposure. For these reasons, MRI is widely used for the non-invasive diagnosis and post-treatment follow-up of primary or secondary tumors, infection, inflammation, vascular and demyelinating or degenerative diseases of the brain and spine in adults and pediatric patients.

Although non-contrast-enhanced MRI is useful in several pathology conditions, CE-MRI is able to provide additional information in a number of brain and spine diseases. It is now widely accepted that CE-MRI increases diagnostic accuracy and confidence, and thus can impact the medical and/or surgical management of patients.

CE-MRI of the CNS relies on disruption of the BBB. Non-specific GBCAs are unable to cross the intact BBB in the normal brain or spine. However, when the BBB is disrupted because of primary or secondary tumors, infection, inflammation, vascular and demyelinating or degenerative diseases of the brain and spine, GBCAs are then able to diffuse through this disrupted BBB. During MRI procedures, contrast is obtained by signal enhancement produced by the paramagnetic metal, gadolinium (Gd^{3+}; also referred to as Gd in this document). Gd^{3+} enhances the magnetic resonance signal by shortening the relaxation times of extracellular water protons in blood and tissues, which results in increased signal intensity in T_1-weighted sequences and reduced signal intensity in T_2-weighted sequences. Since free Gd^{3+} is highly toxic in humans, it must be linked to a complexing agent (ligand) when administered in order to suppress its toxicity and ensure rapid excretion from the body.

3.2 Characteristics of GBCAs for MRI

All GBCAs are made of the same principle components: a gadolinium ion linked to a complexing agent (i.e. the ligand). GBCAs can differ in a number of properties, such as:

- Chemical structure (macrocyclic versus linear [open-chain], ionic versus non-ionic)
- Thermodynamic stability (i.e., the affinity of Gd^{3+} for its ligand)
- Kinetic stability (i.e., time course of dissociation of gadolinium)
- Relaxivity (a measure of their ability to enhance tissue during MRI exams)

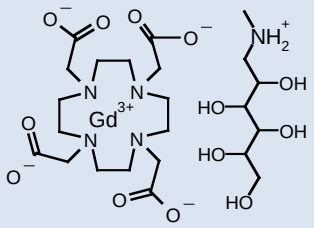
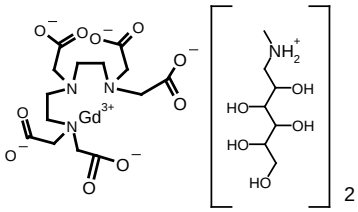
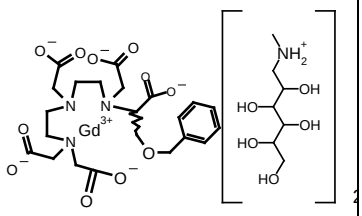
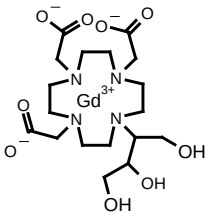
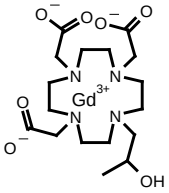
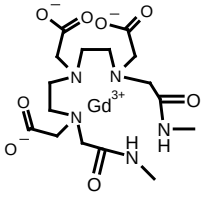
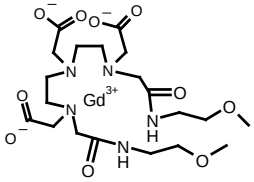
These characteristics are key for safety and diagnostic performance. In particular, the thermodynamic and kinetic stabilities are essential properties that determine the safety profile of GBCAs.

3.2.1 Chemical Structure of Different GBCAs

Based on the structural association of the gadolinium atom with its ligand, currently marketed non-specific GBCAs can be categorized as having either macrocyclic structure or open-chain

structure (Figure 1). Macrocyclic chelates offer strong binding to Gd^{3+} by virtue of their pre-organized, optimally sized rigid ligands that surround the gadolinium atom. Compared to non-ionic GBCAs, ionic chelates are more stable since the binding between Gd^{3+} with the negatively charged carboxyl group is stronger.

Figure 1: Structure of Currently Marketed Gadolinium Chelates Used for CNS MRI

	Macrocyclic*		**Open-chain (linear)****	
Ion-ic	 **Dotarem®** (gadoterate meglumine)		 Magnevist® (gadopentetate dimeglumine)	 MultiHance® (gadobenate dimeglumine)
Non ion-ic	 Gadavist® (gadobutrol)	 ProHance® (gadoteridol)	 Omniscan® (gadodiamide)	 OptiMARK® (gadoversetamide)

Abbreviations: GBCA = gadolinium-based contrast agent; Gd = gadolinium; MRI = magnetic resonance imaging

* Macrocyclic structure (complexes are derived from Tetraazacyclododecanetetraacetic acid [DOTA])

** Open-chain structure (complexes are based on the Diethylenetriaminepentacetate [DTPA] backbone)

3.2.2 Relationship Between Structure, Stability and *in vivo* Gd Dissociation

High stability is desirable for GBCAs, as dissociation of Gd^{3+} from an MRI contrast agent can cause SAEs. When gadolinium disassociates from its chelate resulting in free gadolinium, it can cause both acute and chronic toxicity, and is suggested to be linked with the risk of developing NSF, as described in non-clinical studies presented in Section 10.1. The GBCAs complex stability is characterized by a thermodynamic stability constant (log K_{therm}), the corresponding conditional stability constant at physiological pH (log K_{cond}) and kinetic stability ($T_{1/2}$, dissociation half-life).

3.2.3 Definitions of the Different Stability Parameters

3.2.3.1 Thermodynamic Stability

By definition, as gadolinium is chelated, a thermodynamic equilibrium exists between the gadolinium [Gd], the ligand [L] and the chelate [GdL]. The stability of this equilibrium is expressed as log K_{therm}:

$[Gd^{3+}] + [L] \leftrightarrows [GdL]$ $\qquad K_{therm} = \frac{[GdL]}{[Gd^{3+}] \times [L]}$

As the value of log K_{therm} does not take into account the protonated species, the conditional thermodynamic stability constant log K_{cond} is calculated at pH 7.4 on the basis of log K_{therm} values and protonation constants of the ligand. Consequently, log K_{cond} represents the equilibrium at physiological pH 7.4.

3.2.3.2 Kinetic Stability

The dissociation rates of gadolinium chelates are slow at pH 7.4, but these molecules dissociate much more rapidly in acidic solutions. Consequently, the kinetic stability of the Gd^{3+} chelates is classically studied by measuring the dissociation half-life ($T_{1/2}$) of the Gd complex in acidic media.

In vivo, in order to avoid any likelihood of free gadolinium release, the highest stability, i.e., the highest log K_{cond}, along with the highest kinetic stability ($T_{1/2}$), is desirable.

The thermodynamic and kinetic stability values of the different marketed GBCAs for CNS imaging are presented in Table 1.

Table 1: Thermodynamic and Kinetic Stability Measurements of Gadolinium Chelates

Gadolinium Chelate	Type of Structure	Thermodynamic Stability		Kinetic Stability $T_{1/2}$ at pH 1.0 at 25°C
		log K_{therm}	log K_{cond} (at pH 7.4)	
DOTAREM	Macrocyclic ionic	25.6	19.3	338 hr
GADAVIST	Macrocyclic non-ionic	21.8	14.7	43 hr
PROHANCE	Macrocyclic non-ionic	23.8	17.1	3.9 hr
MULTIHANCE	Open-chain ionic	22.6	18.4	< 5 s
MAGNEVIST	Open-chain ionic	22.1	17.7	< 5 s
OMNISCAN	Open-chain non-ionic	16.9	14.9	< 5 s
OPTIMARK	Open-chain non-ionic	16.6	15.0	< 5 s

Abbreviations: K_{cond} = conditional stability constant at physiological pH; K_{therm} = thermodynamic stability constant; $T_{1/2}$ = half life

Source: Data on file; Port *et al*, 2008.

4 DEVELOPMENT HISTORY OF DOTAREM

Summary:

- Dotarem has been chemically designed to be both a **macrocyclic** and **ionic** GBCA to ensure the highest stability among GBCAs.
- Dotarem was first approved in 1989 (France). CE-MRI of the CNS was the first approved indication and is the most widely used application for Dotarem.
- Dotarem is marketed in vials and pre-filled syringes. To date, approvals have been obtained in more than 70 countries worldwide. In most countries, Dotarem is approved for use in adults and pediatric patients, including neonates and infants. The list of approvals and indications approved per countries is provided in Appendix 1.
- Recommended dose of Dotarem is 0.1 mmol/kg BW, with higher doses up to 0.3 mmol/kg BW approved in many countries for some specific uses.
- Efficacy and safety of Dotarem have been well characterized in a total of 49 clinical studies involving 2813 patients exposed to Dotarem, including 141 pediatric patients between 0 to 17 years of age.
- Safety profile is supported by post-marketing experience from approximately 30 million doses administered since its first approval.

4.1 Current Worldwide Approval Status

Dotarem was first approved in 1989 in France for the indication “contrast-enhanced MRI of the CNS”. Subsequent to this initial approval, Dotarem has been approved in more than 70 countries worldwide, including most European Union countries, Australia, New Zealand, South Korea and Japan (gadoterate meglumine is marketed as Magnescope® in Japan).

Following the initial approvals of Dotarem for use in magnetic resonance of the CNS, Dotarem has been approved for the following applications:

- Contrast-enhanced magnetic resonance angiography (CE-MRA)
- Whole body contrast-enhanced magnetic resonance (includes imaging of liver, pancreas, breast, kidney, and musculoskeletal system)

Furthermore, in almost all the countries Dotarem is approved for use in adults and pediatric patients, including neonates and infants (Appendix 1).

4.2 Approved Dosages

Dotarem is used exclusively via IV administration. The recommended dose is 0.1 mmol/kg BW for all indications.

In MRA, if needed (depending on the results of the examination being performed), a second injection of 0.1 mmol/kg BW may be administered during the same session (total dose 0.2 mmol/kg BW).

For MRI of the CNS, in some countries under certain circumstances (e.g., in the confirmation of isolated brain metastasis or the detection of leptomeningeal tumors), a second injection of 0.2 mmol/kg BW can be administered 20 minutes after the initial dose (total dose 0.3 mmol/kg BW).

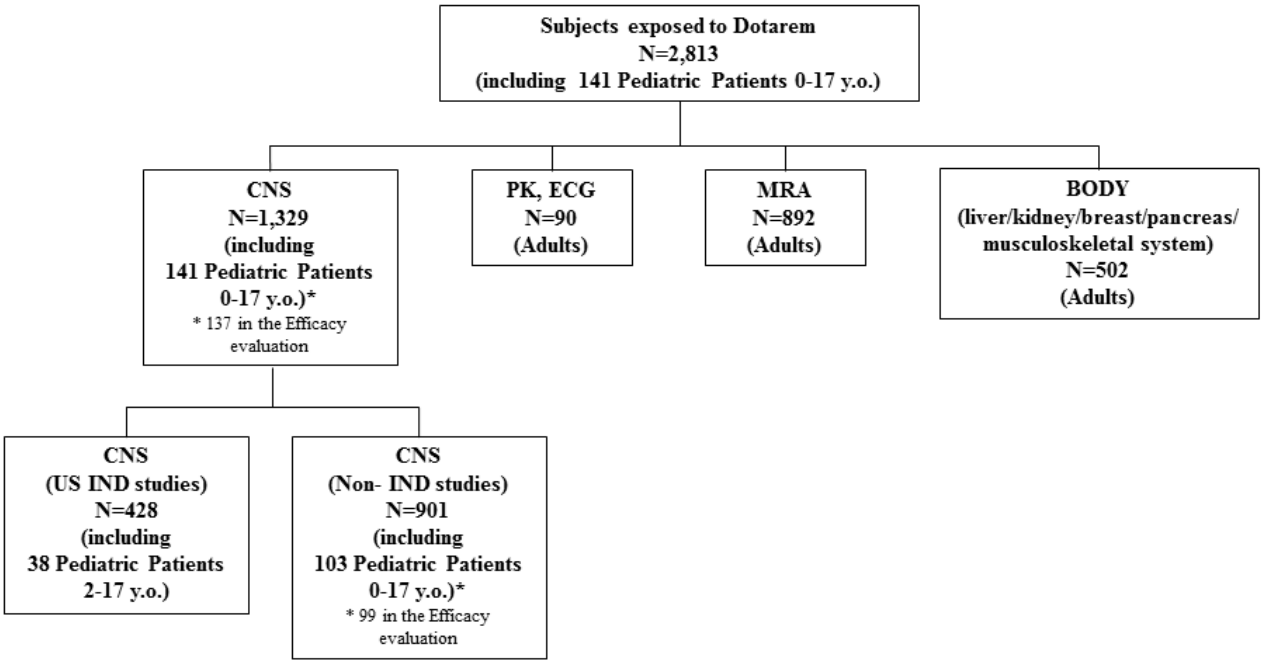
In all pediatric patients, the recommended dose of Dotarem is always 0.1 mmol/kg BW.

4.3 Summary of Clinical Development Program for Dotarem

The NDA includes a total of 49 Guerbet-sponsored clinical studies phase I-IV, enrolling a total of 3364 subjects, of which 2813 subjects were exposed to Dotarem (including 42 healthy volunteers in Phase I studies). The 2813 subjects comprise the overall safety population. Appendix 2 presents a list of these studies. Dotarem efficacy and safety was demonstrated in a broad set of indications.

The clinical development program for Dotarem included in the NDA for the proposed CNS indication and dosage is supported by 2 adequate and well-controlled pivotal Phase III studies, 21 supportive, controlled clinical studies, including 3 pediatric studies. In the 23 controlled CNS clinical studies, the efficacy population includes a total of 1329 patients exposed to Dotarem (including 141 pediatric patients aged 0-17 years). A total of 277 patients received Magnevist (Figure 2).

Figure 2: Dotarem Clinical Development Program (Subjects Exposed to Dotarem)



Abbreviations: CNS = central nervous system; IND = Investigational New Drug (application); MRA = magnetic resonance angiography; PK = pharmacokinetics

In addition to the clinical development program for Dotarem, a total of 6 prospective post-marketing observational studies included 234 children less than 2 years of age.

4.4 Choice of the Indication for the Current Application

Across the countries in which Dotarem is marketed, CE-MRI of the CNS is the most widely used application of this product. Therefore, CNS imaging in adults and pediatric patients has been selected as the first indication proposed for marketing authorization in the US.

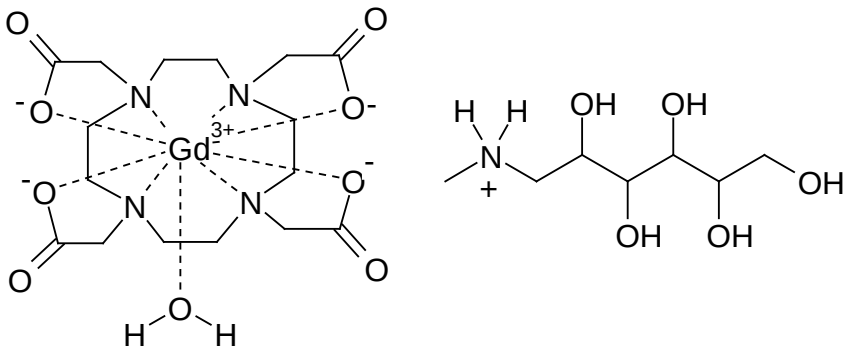
5 PHYSICO-CHEMICAL CHARACTERISTICS OF DOTAREM

Summary:

Dotarem is the only macrocyclic and ionic gadolinium-based contrast agent intended for diagnostic examinations carried out by MRI.

- Dotarem has the highest thermodynamic and kinetic stability among GBCAs. A high kinetic stability combined with a high thermodynamic stability reduces the likelihood of free gadolinium, which is known to be highly toxic.
- The presence of the 7 unpaired electrons in the gadolinium ion Gd^{3+} allows for its paramagnetic activity, with a shortening of the longitudinal relaxation time T1 providing improved image contrast.
- Dotarem has a relaxivity comparable to other currently marketed GBCAs, allowing for signal enhancement and MRI efficacy. The relaxivity of Dotarem is appropriate to enhance brain lesions with a leaky BBB, as demonstrated by clinical studies (e.g., pivotal Phase III studies presented in Section 8.2.1).
- Dotarem is a 0.5 M aqueous injectable solution administered intravenously, as for most marketed GBCAs.
- Dotarem has a stable physico-chemical profile: In over 20 years of experience, no significant change has been observed in stability studies (no free gadolinium ever detected, no degradation impurity ever quantified).
- The structural formula of gadoterate meglumine is presented in Figure 3 (molecular weight of 753.86 g/mol on anhydrous basis).

Figure 3: Gadoterate Meglumine Structural Formula in Aqueous Solution



5.1 Macrocyclic and Ionic Structure

Dotarem presents a chemical structure unique among the GBCAs; it is the only macrocyclic and ionic gadolinium complex. The macrocycle encircles the gadolinium ion, which is strongly bound due to its ionic relationship with the ligand.

5.2 High Stability

The thermodynamic stability constants (log K_{therm} and log K_{cond} at pH 7.4) reflect the affinity of Gd^{3+} for its ligand, and kinetic stability (dissociation $T_{½}$) values reflect the kinetics of potential chelate dissociation. The higher the value of these measurements, the higher the stability of the complex. Different GBCA stability constants are presented in Table 1.

Due to its unique chemical structure, Dotarem presents the highest stability constants for both thermodynamic stability and conditional stability (see Section 3.2.3), as well as the largest kinetic inertness (dissociation $T_{½}$).

5.2.1 Thermodynamic Stability

The high thermodynamic stability of Dotarem is based on 2 factors:

- Macrocyclic structure:

The macrocyclic effect is related to the cavity size of the chelate ring, and also to pre-organization and rigidity of the ligand. Linear open-chain ligands do not benefit from a macrocyclic effect (tight packing of the molecule around the gadolinium ion).

- Ionic structure:

The complex stability is linked to the electrostatic interactions between the gadolinium and the ligand; non-ionic ligands bind more weakly than ionic ones. The higher negative charge of the $DOTA^{4-}$ (tetraazacyclododecanetetraacetic acid) ligand results in a stronger complex. This point is illustrated by the fact that the stability constants (K_{therm} and K_{cond}) of Dotarem are 2 to 4 orders of magnitude higher than those of Prohance and Gadavist, 2 other macrocyclic but non-ionic gadolinium chelates.

5.2.2 Kinetic Stability

High kinetic stability is also an important parameter for understanding potential *in vivo* dissociation that could lead to gadolinium release.

The kinetic stability of Dotarem is linked to its macrocyclic and ionic structure, which ensures both a tight packing of the molecule around the gadolinium ion, and consequently, a high conformational rigidity. As shown in Table 1, Dotarem presents a kinetic stability 8-fold higher than Gadavist (338 h for Dotarem compared to 43 h for Gadavist).

Dotarem, as a macrocyclic and ionic chelate, is the most stable of known GBCAs. This reduces the risk of dissociated gadolinium release *in vivo*, where free gadolinium is strongly suggested to be linked to the risk of triggering NSF.

5.3 Effectiveness of Dotarem for Signal Enhancement

Diagnostic performance of a contrast agent for clinical CNS MRI is evaluated based on safety, blood pharmacokinetics, tissue biodistribution and efficacy in enhancing lesion-to-background signal intensity (contrast-to-noise ratio).

The contrast of a magnetic resonance image results from a complex interaction of various factors such as T1 and T2 relaxation times, proton density, magnetic field and MRI sequences. MRI contrast agents are used in MRI to decrease the longitudinal (T1) and transverse (T2) relaxation times of water protons present in the tissues.

Among all the physico-chemical properties characterizing a gadolinium-chelate, the efficacy of an MRI contrast agent is measured in terms of relaxivities, i.e., the longitudinal (r1) and transverse (r2) relaxation rates of the water protons observed at a millimolar concentration of contrast agent. These 2 parameters are acting in simultaneous, but opposing ways on the signal enhancement:

- r1 induces a positive effect on signal enhancement (namely "T1 effect"), which is seen as brightening.
- r2 induces a negative effect on signal enhancement (namely "T2 effect"), which is seen as darkening.

In Table 2, typical relaxivities of marketed contrast agents are reported. The T1 effectiveness of Dotarem is in the same range of other marketed non-specific GBCAs.

With this relaxivity, the resulting T1 enhancing effect is significant. For example, for a basal T1 of 1.11 sec, which is typical of natural brain T1 at 1.5T (Stanisz *et al.*, 2005) and for a mean concentration of 0.12 mM Dotarem in a brain tumor (Le Duc *et al.*, 2004), the T1 is reduced of 29%, from 1.11 second to 0.79 second (Table 2) (according to the equation: $1/T1_{post}=1/T1_{pre}+ r1.C$, where $T1_{post}$ is the T1 after injection, $T1_{pre}$ is the T1 before injection and C is the estimated mean concentration in a brain tumor 10 minutes after injection of 0.1 mmol/kg of GBCA).

Moreover, relaxivity of Dotarem is stable over the range of magnetic fields used in radiological practice (Laurent *et al.*, 2006).

Overall, Dotarem has a relaxivity comparable to the other currently marketed GBCAs, ensuring optimal signal enhancement and MRI efficacy. The relaxivity of Dotarem is appropriate to enhance brain lesions with abnormal, leaky BBB, as demonstrated by clinical studies (e.g., pivotal Phase III studies, Section 7.2.1).

Table 2: Relaxivities at 1.5T and 37°C for the Currently Marketed GBCAs

Gadolinium Chelate	Type of Structure	r1 ($mM^{-1}.s^{-1}$)	r2 ($mM^{-1}.s^{-1}$)	Calculated % of reduction of brain T1 at a 0.12 mM tissue concentration	
				ΔT1 (%)	[min ; max] * (%)
DOTAREM	Macrocyclic ionic	3.0	3.5	29 %	[26 ; 31]
GADAVIST	Macrocyclic non-ionic	3.3	3.9	31 %	[29 ; 32]
PROHANCE	Macrocyclic non-ionic	2.9	3.4	28 %	[25 ; 30]
MULTIHANCE	Open-chain ionic	3.8	4.4	33 %	[32 ; 35]
MAGNEVIST	Open-chain ionic	3.3	3.9	31 %	[29 ; 32]
OMNISCAN	Open-chain non-ionic	3.3	3.9	31 %	[29 ; 32]
OPTIMARK	Open-chain non-ionic	3.6	4.1	32 %	[31 ; 34]

Abbreviations: GBCA = gadolinium-based contrast agent; Gd = gadolinium;

Source: Relaxivities data from Port *et al.*, 2008.

* Min and max values of post-injection ΔT1 are calculated from the uncertainty of relaxometric measurements ($\pm 0.3\ mM^{-1}.s^{-1}$)

5.4 Concentration, Osmolality and Viscosity

The concentration of gadoterate meglumine in Dotarem pharmaceutical solution is 0.5 mol/L.

The osmolality of Dotarem is linked to its ionic structure. Dotarem presents the smallest osmolality among ionic GBCAs (MultiHance and Magnevist) (Table 3). Considering the low amount of injected dose, the osmolality level is fully compatible with IV injection. The increase in plasma osmolality after injection of a 0.1 mmol/kg dose is considered clinically insignificant (Port *et al.*, 2008).

The viscosity of Dotarem is compatible with IV injection and is also lower than MultiHance, Gadavist and Magnevist.

Table 3: Osmolality and Viscosity of Currently Marketed GBCAs at 37°C

Gadolinium Chelate	Type of Structure	Osmolality at 37°C (mOsm/kg H_2O)	Viscosity at 37°C (mPa.s)
DOTAREM	Macrocyclic ionic	1350	2.4
GADAVIST	Macrocyclic non-ionic	1603	5.0
PROHANCE	Macrocyclic non-ionic	630	1.3
MULTIHANCE	Open-chain ionic	1970	5.3
MAGNEVIST	Open-chain ionic	1960	2.9
OMNISCAN	Open-chain non-ionic	789	1.4
OPTIMARK	Open-chain non-ionic	1110	2.0

Abbreviations: GBCA = gadolinium-based contrast agent; mOsm = milliosmols; mPa.s = milliPascal-second
Sources: Data on file and US Package Inserts

6 NON-CLINICAL DEVELOPMENT

Summary:

Based on the results of the non-clinical studies, Dotarem is not expected to induce any severe or irreversible adverse effects in humans after an IV bolus injection at the recommended dose (0.1 mmol/kg). The following observations and conclusions were made from non-clinical studies after IV injection:

- Dotarem is rapidly distributed in the blood volume and extracellular fluid. It is not bound to plasma proteins and is rapidly excreted unchanged in urine.
- Dotarem did not cause adverse effects on any main physiological functions when administered at the clinical dose level. Only minor and transient effects were observed at dose levels that were much higher than the recommended human dose (Section 6.3.1).
- No safety concerns arose from single-dose and repeat-dose toxicology studies.
- Dotarem is not mutagenic.
- No effect on mating performance and fertility (rats) and no teratogenicity or embryotoxicity (rats and rabbits) were observed after repeated injections of several times the recommended human dose.
- Local tolerance of Dotarem was found to be satisfactory, even in case of misadministration outside the vein (extravasation).
- A very low risk of NSF is anticipated for Dotarem, based on its high kinetic and thermodynamic stability and the lack of free Gd release observed in non-clinical studies. This is fully consistent with clinical studies and post-marketing experience, as no single-agent cases of NSF has been reported in humans with Dotarem after approximately 30 million exposures since initial approval in 1989.

6.1 Pharmacological Class and Pharmacodynamics

As described in Section 3, Dotarem is a macrocyclic and ionic GBCA for MRI. The Gd ion has paramagnetic properties due to its 7 unpaired electrons, leading to high magnetic spin moment and labile water coordination properties. Gd enhances the magnetic resonance signal by shortening relaxation times of extracellular water protons in blood and tissues, which results in increased signal intensity in T_1-weighted sequences and reduced signal intensity in T_2-weighted sequences. To suppress the toxicity of free Gd ion and ensure a rapid excretion from the body, Gd is chelated by a ligand (DOTA in Dotarem). The relaxivity values of Dotarem were presented in Table 2.

6.2 Non-clinical Pharmacokinetics

Pharmacokinetics of Dotarem were studied in rats, rabbits, dogs and goats after IV injection. Dotarem is distributed rapidly in the extracellular space, does not cross the intact BBB, is not bound to proteins and is not metabolized. Pharmacokinetic parameters, including human

clinical data for reference, are presented in Table 4. It is eliminated predominantly in urine in a few hours and is dialyzable. Negligible amounts cross the placenta and are excreted in milk (similar to other agents). No relevant gender difference was observed. In the studies in which Magnevist was used as a comparator, Dotarem exhibited a similar pharmacokinetic profile.

Table 4: Pharmacokinetic Parameters of Dotarem

	Rat	Rabbit	Rabbit	Dog	Goat	Human[a] (men)	Human[a] (men)	Human[a] (men)	Human (women)
Dose (mmol/kg)	0.1	0.1	0.5	0.1	0.086	0.1	0.1	0.1	0.1
$T_{1/2\alpha}$ (min)	NA	5.3	6.5	2	NA	6	7	NA	NA
$T_{1/2\beta}$ (min)	18	38	58	68	50	72	78	120	83
Vd (mL/kg)	88[b]	132	191	271	330	177	171	284	210
Cl_T (mL/min/kg)	NA	NA	NA	NA	NA	1.7	1.6	1.6	1.7
Cl_R (mL/min/kg)	NA	1.9	2.4	5.0	NA	1.6	NA	1.4	1.3

Abbreviations: Clr = renal clearance; Clt = total clearance; NA = not available; T1/2 = half-life; Vd = distribution volume

[a] Several studies / Publication Matsuyama, 1994

[b] mL instead of mL/kg

6.3 Non-Clinical Safety

6.3.1 Safety Pharmacology

The safety pharmacology evaluation of Dotarem included studies in the CNS, the cardiovascular, respiratory and renal systems, red blood cells and various *in vitro* experimental models involving calcium-dependent systems. In all studies conducted, Dotarem was well tolerated at dose levels similar to, or several times higher than, the recommended diagnostic dose in humans. When Magnevist was used as a reference compound, Dotarem exhibited a similar or better profile.

With Dotarem, the main findings (mostly attributed to the hyperosmolarity of the solution) were the following:

- Minor pro-convulsive effects at high doses in mice at 4 mmol/kg (i.e., 40 times the clinical dose, or 3.2 times after adjustment for body surface area).
- Moderate and transient decrease of heart rate, increase of arterial blood pressure and renal blood flow at 1 mmol/kg in dogs (i.e., 10 times the clinical dose, or 5.4 times after adjustment for body surface area).
- Moderate and transient increase in urine creatinine, urea, albumin and lactate dehydrogenase without signs of alteration of the glomerular function at 1 mmol/kg in dogs (i.e., 10 times the clinical dose, or 5.4 times after adjustment for body surface area).

- *In vitro*, there was no histamine or serotonin release from rat peritoneal mast cells. Otherwise, *in vitro*, the following effects were observed at high concentrations (>50 times the human maximum concentration [C_{max}]) so they are very unlikely to occur in humans:
    - Moderate increase in coagulation time and partial inhibition of platelet aggregation
    - Slight reduction in deformability of erythrocytes
    - Decrease in hemolytic activity of the complement and of the anaphylatoxin C3a production

There was no effect on ECG, specifically QT interval, and no effect on cardiac action potential in dog Purkinje fibers. A subsequent clinical thorough QT study did not show clinically relevant effects at 0.1 mmol/kg and at a cumulative dose of 0.3 mmol/kg (0.1 + 0.2 mmol/kg).

6.3.2 Toxicology

6.3.2.1 Single-Dose Toxicity

Acute toxicity of Dotarem after IV administration was low, whatever the species. No mortality occurred in rats and dogs at dose levels representing 24 and 40 times the intended diagnostic dose in humans, respectively, adjusted for body surface area. The main finding was a dose-related vacuolization of tubular epithelial cells in kidneys. This effect is classically described for all GBCAs, as well as with iodinated contrast agents, and is known to have no physiological consequence on kidney function.

6.3.2.2 Repeat-Dose Toxicity

As in single-dose studies, administration of Dotarem in rats and dogs at daily doses as much as 13 times higher than clinical dose (after adjustment for body surface area), and for 28 days, induced mainly vacuolization of renal proximal tubular epithelial cells, generally associated with an increased kidney weight. No skin change or NSF-like lesions were observed.

6.3.2.3 Genotoxicity

Dotarem was not mutagenic *in vitro* (Ames test, chromosomal aberration assay in Chinese hamster ovary cells, gene mutation assay in V79 Chinese hamster cells) and *in vivo* (micronucleus test in mice by IV route).

6.3.2.4 Reproductive and Developmental Toxicity

Dotarem was not embryotoxic or teratogenic in female rats or rabbits and had no effect on mating performance and fertility in male and female rats when given under drastic administration conditions (doses up to 23 times the intended dose in human, adjusted for body surface area, given daily over several weeks). Maternal toxicity, characterized by a decrease of body weight or a lower body weight gain, was observed in both rats and rabbits, but at a higher severity in rabbits and at very high doses (≥10 times the human dose after adjustment for body surface area), far from the intended conditions of use in human (dose

and number of injections). A slight delay in fetal ossification may be attributed to Dotarem, but is likely a consequence of maternal toxicity.

6.3.2.5 Juvenile Toxicity

No toxicology study was conducted in juvenile animals. Guerbet is currently in the process to perform a study in neonate rats and has submitted a study protocol to the FDA for comments in December 2012. The study has a proposed start date of January 2013, and an audited draft report will be available during the 3rd quarter of 2013.

6.3.3 Local Tolerance

Macroscopic and microscopic findings at the injection sites after IV, perivenous, intra-arterial, subcutaneous and intra-muscular administration of Dotarem were similar between control and treated animals, and were considered to be due to the administration procedure, and not related to Dotarem. Slight irritation was locally induced after perivenous injection in rabbits, but this effect was not associated with any histopathological signs of necrosis.

Local tolerance of Dotarem was found to be satisfactory in animal models, even in cases of misadministration outside the vein.

6.3.4 Allergenicity

Active systemic anaphylaxis and passive cutaneous anaphylaxis were tested with Dotarem in guinea pigs. All these tests were negative for Dotarem.

6.3.5 Non-Clinical Studies Related to the Risk of NSF

Several non-clinical studies were performed to better understand the mechanisms that trigger NSF after administration of GBCAs. These studies showed that the potential for Dotarem to trigger NSF is very low due to its high stability, even in animals with impaired renal function. These studies are described in details in Section 10.1.

7 CLINICAL PHARMACOLOGY

Summary:

- After IV injection, Dotarem is rapidly distributed in blood and extracellular fluid. It is rapidly excreted in urine in subjects with normal renal function, as for all GBCAs.
- Urinary elimination is delayed with renal impairment.
- No dose adjustment is required for any patient population.
- Dotarem does not induce any modification of ECGs and does not induce QT/QTc interval prolongation.

7.1 Pharmacokinetics in Healthy Volunteers

Two pharmacokinetic studies were conducted by Guerbet with Dotarem on healthy volunteers. The dose levels studied were 0.1 mmol/kg, or 0.1 followed by 0.2 mmol/kg 20 minutes after the first injection. One study included only men, while the other study included both men and women. Furthermore, an independently conducted PK study involved Japanese men healthy volunteers (Matsuyama, 1994). The pharmacokinetic parameters and profile were consistent across studies.

7.1.1 Absorption

Absorption is not applicable since Dotarem is given solely via IV administration.

7.1.2 Distribution

Pharmacokinetic parameters in humans are presented in Table 5. The volume of distribution of Dotarem was roughly equivalent to that of extracellular fluid. Within the studied dose range (0.1 to 0.3 mmol/kg), the kinetics of Dotarem appear to be linear.

Dotarem does not undergo significant protein binding *in vitro*. The extent of blood cell partitioning of Dotarem is not known.

7.1.3 Metabolism

Dotarem is not metabolized.

7.1.4 Excretion

Dotarem is eliminated from plasma with a mean terminal $T_{1/2}$ of about 1.4 ± 0.2 hrs and 2.0 ± 0.7 hrs in female and male subjects, respectively. Dotarem, administered at 0.1 mmol/kg, is rapidly excreted primarily in the urine, with 72.9 ± 17.0% and 85.4 ± 9.7% (mean ± SD) eliminated within 48 hrs in female and male subjects, respectively. Similar values were achieved after a cumulative dose of 0.3 mmol/kg (0.1 + 0.2 mmol/kg), with 85.5 ± 13.2% and 92.0 ± 12.0% recovered in urine within 48 hrs in female and male subjects, respectively.

In healthy subjects, the renal and total clearances of Dotarem are very similar (Table 5), indicating that the drug is essentially cleared through the kidneys via glomerular filtration.

7.2 Pharmacokinetics in Special Populations

7.2.1 Age, Gender and Race

The effects of age on the pharmacokinetics of Dotarem was not specifically studied (see Section 7.2.2, Renal Impairment).

There were no relevant differences in pharmacokinetics regarding gender.

The influence of race on pharmacokinetics was not studied, but no effect is expected due to the lack of protein binding or metabolism of Dotarem.

7.2.2 Renal Impairment

Phamacokinetics of Dotarem was studied in patients with either moderate (30-60 mL/min creatinine clearance) or severe (10-30 mL/min creatinine clearance) renal impairment, compared with healthy volunteers. Total clearance of Dotarem decreased as a function of the degree of renal failure. The distribution volume was unaffected by the severity of renal failure (Table 55). No changes in renal function test parameters were observed after Dotarem injection. The mean cumulative urinary excretion of Dotarem was approximately 93.3 ± 4.7% in 24 hrs for subjects with normal renal function, 76.9 ± 4.5% in 48 hrs in patients with moderate renal impairment and 68.4 ± 3.5% in 72 hrs in patients with severe renal impairment.

No dosage adjustment is recommended for patients with renal impairment. However, caution is required in this population, especially in cases of severe renal impairment, due to the potential risk of NSF.

Dotarem is dialyzable.

Table 5: Pharmacokinetic Profile in Healthy Subjects and Renally Impaired Patients

Population	Elimination Half-life (hr)	Plasma Clearance (L/h/kg)	Distribution Volume (L/kg)
Healthy volunteers (n=4)	1.6 ± 0.2	0.10 ± 0.01	0.246 ± 0.03
Patients with moderate renal impairment (n=4)	5.1 ± 1.0	0.036 ± 0.007	0.236 ± 0.01
Patients with severe renal impairment (n=4)	13.9 ± 1.2	0.012 ± 0.001	0.234 ± 0.01

7.2.3 Hepatic Impairment

The influence of hepatic impairment on the pharmacokinetics of Dotarem was not specifically studied, but no effect is expected as Dotarem is not metabolized.

7.2.4 Pediatric Population

There were no pharmacokinetic studies conducted in pediatric patients. No dosage adjustment is recommended for pediatric patients (0 to 17 years of age) in any countries where Dotarem is approved.

7.3 Drug-Drug Interaction Potential

No specific drug-drug interaction studies have been conducted, but such interactions have never been reported in post-marketing experience and are very unlikely due to the high water solubility of the drug and the lack of protein binding or metabolism of Dotarem.

7.4 Thorough QT Study

A double-blind, placebo-controlled, cross-over randomized study was conducted in 40 patients aged 18 to 85 years suffering from a disease for which a contrast-enhanced T1 MRI examination could be required. The primary objective was to evaluate the electrocardiographic safety of Dotarem (particularly in terms of QT interval changes) in patients after IV bolus.

All patients received both placebo and Dotarem during two 24-hr periods, separated by a wash-out of at least 2 days. Dotarem was administered as an IV bolus of 0.1 mmol/kg, followed by a second injection of 0.2 mmol/kg 20 minutes after the first dose.

Dotarem had no effect on the QT or QTc interval or other ECG parameters after bolus IV administration of a cumulative dose of 0.3 mmol/kg.

8 EFFICACY

Summary:

The efficacy of Dotarem in MRI of the CNS has been demonstrated in 2 adequate and well-controlled pivotal Phase III studies. All defined primary and key secondary efficacy analyses were positive and support the efficacy of Dotarem at a standard dose of 0.1 mmol/kg BW.

Statistically significant superiority in lesion visualization on "Paired" images (unenhanced plus Dotarem-enhanced MRI) over "Pre" images (unenhanced MRI) was demonstrated across all readers and in both studies, for all three co-primary endpoints:

- Lesion border delineation
- Lesion internal morphology
- Lesion contrast enhancement

In addition to these 2 pivotal studies, 21 supportive clinical studies concurred with the efficacy of Dotarem-enhanced MRI. Supportive studies showed that Dotarem-enhanced images were superior to unenhanced images with regard to clinically relevant imaging parameters.

Regarding specifically the pediatric population from 0 to 17 years of age, efficacy of Dotarem in the CNS indication was assessed in pivotal study DGD-44-050 and in 3 open-label, single-group, non-randomized studies (DGD-3-15, DGD-3-16 and DGD-3-29). Efficacy results obtained in the pediatric population were consistent with those obtained in the adult population. Dotarem-enhanced MRI produced significant improvement in the ability to detect and visualize CNS lesions and the overall image quality.

Dotarem, administered at the recommended dose of 0.1 mmol/kg BW, improves diagnostic capabilities over unenhanced MRI alone for detection and visualization of CNS lesions in both adult and pediatric populations.

A specific analysis of efficacy in pediatric patients less than 2 years of age is provided in Section 11.

8.1 General Aspects of CNS Imaging

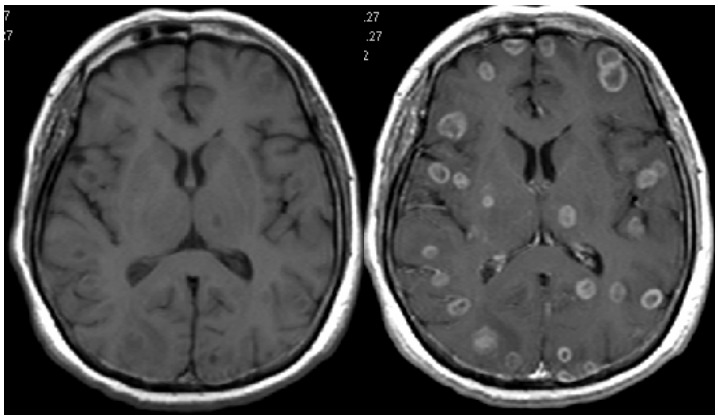
8.1.1 Diagnosing of CNS Lesions

CE-MRI utilizes non-specific GBCAs as the clinical standard for detecting and delineating most intracranial or spinal lesions and lesions in associated tissues. It relies on the disruption of the BBB. The brain and spine are surrounded by a BBB, which is both a physical barrier and a cellular transport system. Normally it maintains homeostasis of the CNS by restricting the entrance of potentially harmful foreign substances from the blood and by allowing the passage of essential nutrients. Non-specific GBCAs are unable to cross the intact BBB. Pathologies of the CNS, such as primary or metastatic brain tumors, stroke and inflammation cause local disruption of the BBB. Contrast agents are able to diffuse through the disrupted

BBB into lesions, resulting in increased signal intensity on contrast-enhanced magnetic resonance images.

Figure 4 shows a representative pair of images taken from the same patient. Examination of the unenhanced image illustrates the presence of several suspicious areas of decreased signal intensity in both cerebral lobes. Without contrast enhancement, some of these lesions may be missed entirely or may be poorly characterized, leading to uncertainties in the diagnosis of a metastatic disease. In comparison, the contrast-enhanced image clearly shows brightly enhanced lesions. The ring-like positive enhancement pattern observed in these lesions indicates that the lesions have vascular borders, and the lack of enhancement in the center of the lesions is indicative of central necrosis.

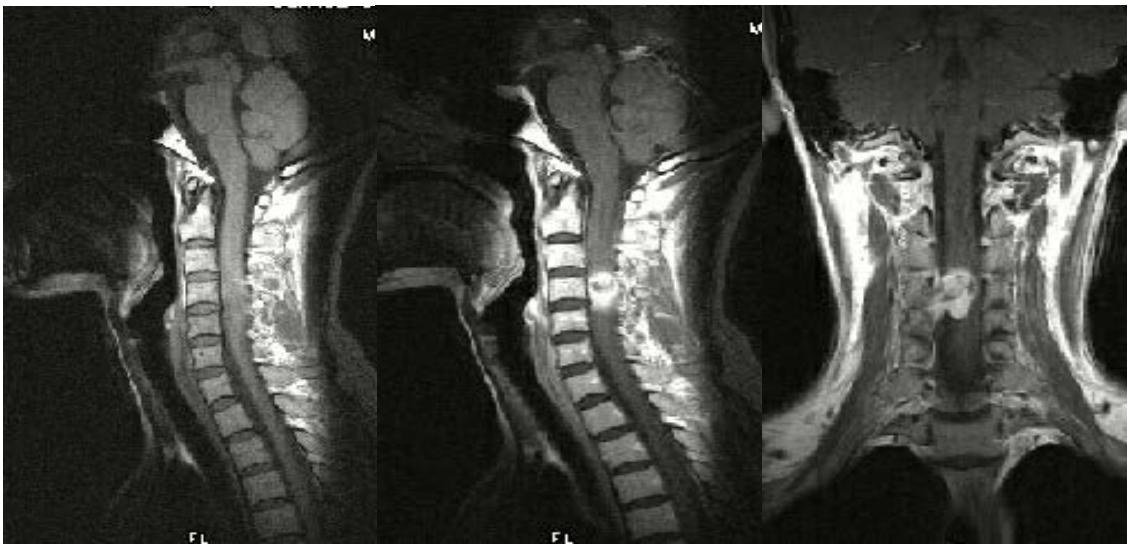
Figure 4: Sample Image Set of a Patient with Brain Metastasis



Pre-contrast (Axial) Post-contrast (Axial)

Spine tumors are relatively rare, but are of great importance due to their potentially devastating clinical effects and their challenging radiographic appearance. Figure 5 shows a schwannoma located in the cervical spine. The tumor is barely seen on an unenhanced image, but contrast-enhanced images show inhomogeneous enhancement of the tumor clearly located in intradural-extramedullary space. The information obtained from CE-MRI can lead radiologists to a reasonable differential diagnosis for tumors occurring in this region.

Figure 5: Sample Image Set of a Patient with Cervical Spine Tumor



Pre-contrast (Sagittal) Post- contrast (Sagittal) Post- contrast (Coronal)

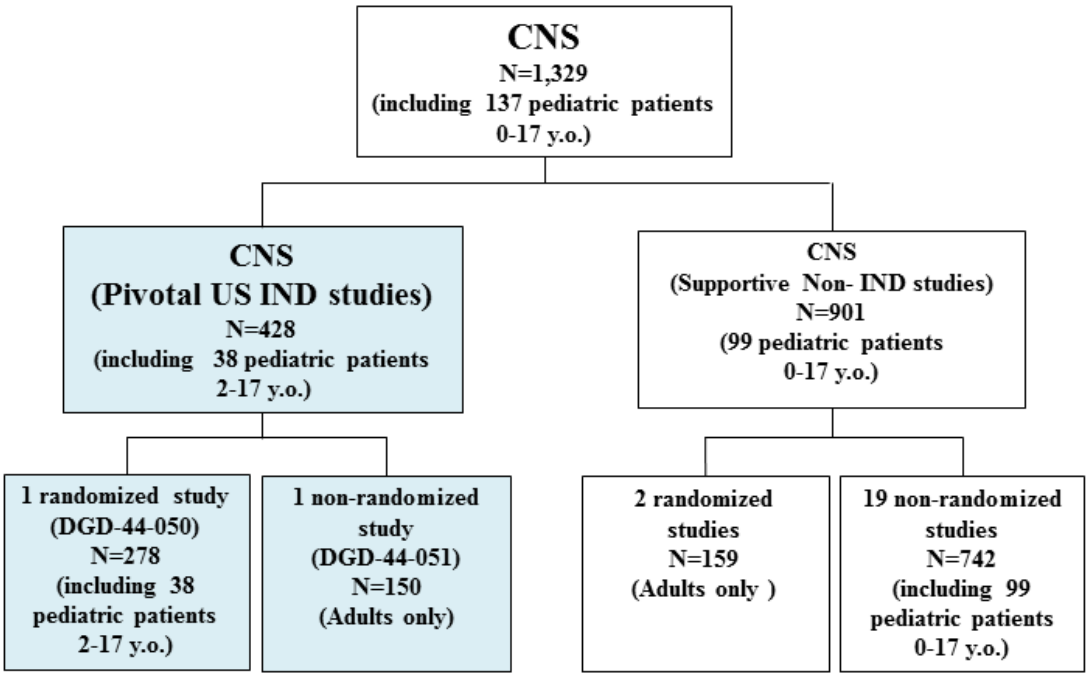
These two examples clearly illustrate the benefit of contrast-enhanced MRI. The enhancement pattern seen in brain and spine lesions following the administration of contrast is key to making a correct diagnosis and is why CE-MRI is the standard of practice for assessing CNS lesions.

8.2 Dotarem Development Program Overview

A total of 49 clinical studies have been completed during the development of Dotarem, enrolling a total of 3364 patients, of which 2813 patients were exposed to Dotarem (including 42 healthy volunteers in phase I studies; Figure 2).

The clinical development program for Dotarem efficacy in the proposed CNS indication and dosage is supported by 2 adequate and well-controlled pivotal phase III studies, 21 supportive, controlled clinical studies, including 3 pediatric studies (Figure 6). In the 23 controlled CNS clinical studies, a total of 1329 patients received Dotarem (including 137 pediatric patients evaluated for efficacy) and 277 received Magnevist.

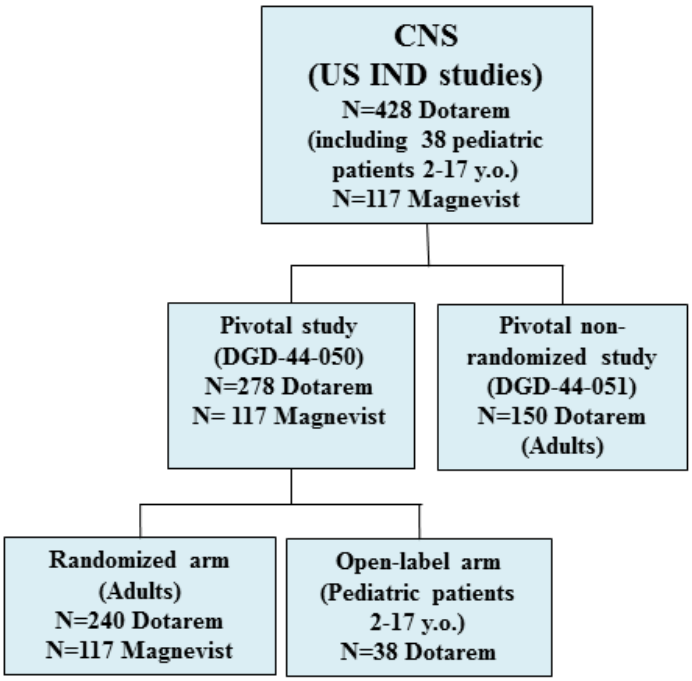
Figure 6: Breakdown of Patients Exposed to Dotarem included in Efficacy Population (0-2 y.o., 2-17 y.o., and adults)



8.2.1 Pivotal Studies in Adults and in Pediatric Patients over 2 Years of Age (CNS)

Figure 7 presents the 2 pivotal phase III studies in patients with known or suspected CNS lesions. Overall, the 2 studies enrolled a total of 507 adult patients (390 exposed to Dotarem and 117 exposed to Magnevist) and 38 pediatric patients (2-17 years of age) exposed to Dotarem.

Figure 7: Breakdown of Patients in Pivotal Phase III Studies



Study DGD-44-050 enrolled 395 patients (240 adults treated with Dotarem, 38 pediatric patients treated with Dotarem, and 117 adults treated with Magnevist) in a prospective, randomized, double-blind, parallel-group, positive-control study of Dotarem versus Magnevist. This multicenter study was conducted in United States, South Korea, Europe and South America in 2010-2011. Dotarem and Magnevist were given IV at 0.1 mmol/kg.

Study DGD-44-051 was a blinded re-read of MRI images originally obtained during the course of Study DGD-3-44, which was conducted under US IND in France and Germany in 2003-2004. The study included 150 adult patients. The scoring system was the same as that used to evaluate MRI images generated in pivotal Study DGD-44-050.. Dotarem was given IV at 0.1 mmol/kg.

8.2.2 Supportive Clinical Studies in Adults (CNS)

Dotarem has been evaluated in 18 additional studies in adults, including 2 randomized, double-blind, parallel-group clinical studies involving 318 patients (159 received Dotarem; 159 received Magnevist), and a series of 16 open-label, non-randomized, single-group clinical studies that involved a total population of 643 adult patients.

All these patients underwent MRI procedures for the diagnosis of various suspected cerebral lesions, the detection of local recurrence of disease, the exploration of the anatomical structure of lesions or as a routine procedure for therapeutic follow up (Table 6).

Table 6: Overview of Supportive Clinical Studies in CNS

Study Identifier / Phase	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects and Type of Population	Country; Study Period
Randomized Clinical Studies					
DGD-3-17 Phase II/III	Comparative diagnostic efficacy and safety	Single center, randomized, double-blind, parallel groups; MRI pre- and post-Dotarem or Magnevist	Dotarem; 0.1 mmol/kg or Magnevist; 0.1 mmol/kg; intravenously	10 patients per group; all with known or suspected CNS lesions	France; 1988
DGD-3-31 Phase III/IV	Comparative diagnostic efficacy and safety	Multicenter, randomized, double-blind, parallel groups; MRI pre- and post-Dotarem or Magnevist	Dotarem; 0.1 mmol/kg or Magnevist; 0.1 mmol/kg; intravenously	149 patients received Dotarem; 149 received Magnevist; all with known or suspected CNS lesions	France, Belgium, Switzerland; 1989
Non-randomized Clinical Studies					
DGD-3-01 Phase II	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	10 patients with known or suspected CNS lesions	France; 1987
DGD-3-03 Phase II	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	30 patients with known or suspected CNS lesions	France; 1987-1988
DGD-3-04 Phase II	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	20 patients with known or suspected CNS lesions	France; 1987
DGD-3-05 Phase II	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	10 patients with known or suspected CNS lesions	Belgium; 1987-1988
DGD-3-07 Phase II	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	56 patients with known or suspected CNS lesions	France; 1986-1987
DGD-3-08 Phase III	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	54 patients with known or suspected CNS lesions	France; 1987
DGD-3-09 Phase II	Efficacy and safety	Open-label, single group MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	22 patients with known or suspected CNS lesions	Belgium; 1987-1988
DGD-3-11 Phase II	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	19 patients with known or suspected CNS lesions	France; 1987-1988

Abbreviations: CNS = central nervous system; MRI = magnetic resonance imaging

Study Identifier / Phase	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects and Type of Population	Country; Study Period
DGD-3-12 Phase II	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	50 patients with known or suspected CNS lesions	France; 1987
DGD-3-14 Phase III	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	55 patients with known or suspected CNS lesions	France; 1987
DGD-3-20 Phase III	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	48 patients with known or suspected Neuro-ophthalmo-logic lesions	France; 1988
DGD-3-21 Phase III	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	50 patients with known or suspected CNS lesions	France; 1987-1988
DGD-3-23 Phase III	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	50 patients with known or suspected CNS lesions	France; 1988
DGD-3-33 Phase III	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; followed by 0.2 mmol/kg 30 minutes later; intravenously	65 patients with known or suspected CNS lesions	France, Belgium; 1994-1995
DGD-3-34 Phase III	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; followed by 0.2 mmol/kg 30 minutes later; intravenously	45 patients all with known or suspected CNS lesions	France, Switzer-land; 1994-1995
DGD-3-40 Phase IV	Efficacy and safety	Open-label, multicenter, single group; MRI pre- and post-Dotarem	0.2 mmol/kg	59 patients with Alzheimer's disease	France, Belgium, Luxemburg, Switzer-land; 1999-2000

Abbreviations: CNS = central nervous system; MRI = magnetic resonance imaging

8.2.3 Clinical Studies Conducted in Pediatric Patients

A total of 38 pediatric patients (from 2-17 years of age) were included in an open-label arm of pivotal Study DGD-44-050.

Additionally, Dotarem efficacy has also been evaluated in 3 open-label, single-group clinical studies that involved 99 pediatric patients, ages 1.2 months through 17 years, who received Dotarem during the course of MRI procedures for the diagnosis of various suspected cerebral lesions, the detection of local recurrence of disease, the exploration of the anatomical structure of lesions or as a routine procedure for therapeutic follow-up (Table 7).

All pediatric age ranges were represented in the 137 pediatric patients evaluated for Dotarem efficacy (7 patients aged <24 months, 33 aged 2-5 years, 57 aged 6-11 years and 40 aged 12-17 years).

Table 7: Overview of Clinical Studies Conducted in Pediatric Patients

Study Identifier	Objectives of the Study	Study Design and Type of Control	Dotarem Dosage Regimen; Route of Administration	Number of Subjects and Type of Population	Country; Study Period
DGD-44-050 Phase III	Efficacy and safety	Open-label arm, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	38 pediatric patients with known or suspected CNS lesions	US, South America; 2010-2011
DGD-3-15 Phase II	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	29 pediatric patients with known or suspected CNS lesions	France; 1988
DGD-3-16 Phase II	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	20 pediatric patients with known or suspected CNS lesions	France; 1988
DGD-3-29 Phase IV	Efficacy and safety	Open-label, single group; MRI pre- and post-Dotarem	0.1 mmol/kg; intravenously	50 pediatric patients with known or suspected CNS lesions	France; 1990-1991

Abbreviations: CNS = central nervous system; MRI = magnetic resonance imaging

8.3 Pivotal Phase III Studies (CNS)

Two adequate and well-controlled Phase III studies were conducted to demonstrate the efficacy and safety of Dotarem in CNS imaging:

- **Study DGD-44-050 – Comparative randomized study:** Safety and efficacy evaluation of Dotarem in MRI in patients with CNS lesions.
- **Study DGD-44-051 - Open-label study:** Blinded centralized re-reading of a Phase III study (protocol DGD-3-44, evaluation of MRI with Dotarem in the diagnosis or follow-up assessment of cerebral or spinal tumors).

Both studies addressed FDA guidelines requiring the demonstration of improvement of the diagnostic information obtained with the combined unenhanced and contrast-enhanced images over images obtained using the MRI device alone.

8.3.1 Special Protocol Assessment (SPA)

The protocol for Study DGD-44-050 was submitted to the US Food and Drug Administration (FDA) for a Special Protocol Assessment (SPA). Through this process, a letter of concurrence was received on 29 July 2010, prior to initiation of the study. This letter of concurrence confirms FDA's agreement that the design and statistical analysis plan of clinical Study DGD-44-050 would support submission of an NDA to seek a CNS imaging indication for Dotarem. The efficacy analyses that were agreed in the SPA for Study DGD-44-050 were duplicated in the re-read Phase III Study DGD-44-051.

8.3.2 Design of the Pivotal Phase III Studies

During discussions of the phase III study designs for the protocol DGD-44-050, the FDA agreed to the study design involving 2 randomized parallel arms in adult patients (Dotarem versus Magnevist) and one open-label arm in pediatric patients (Dotarem).

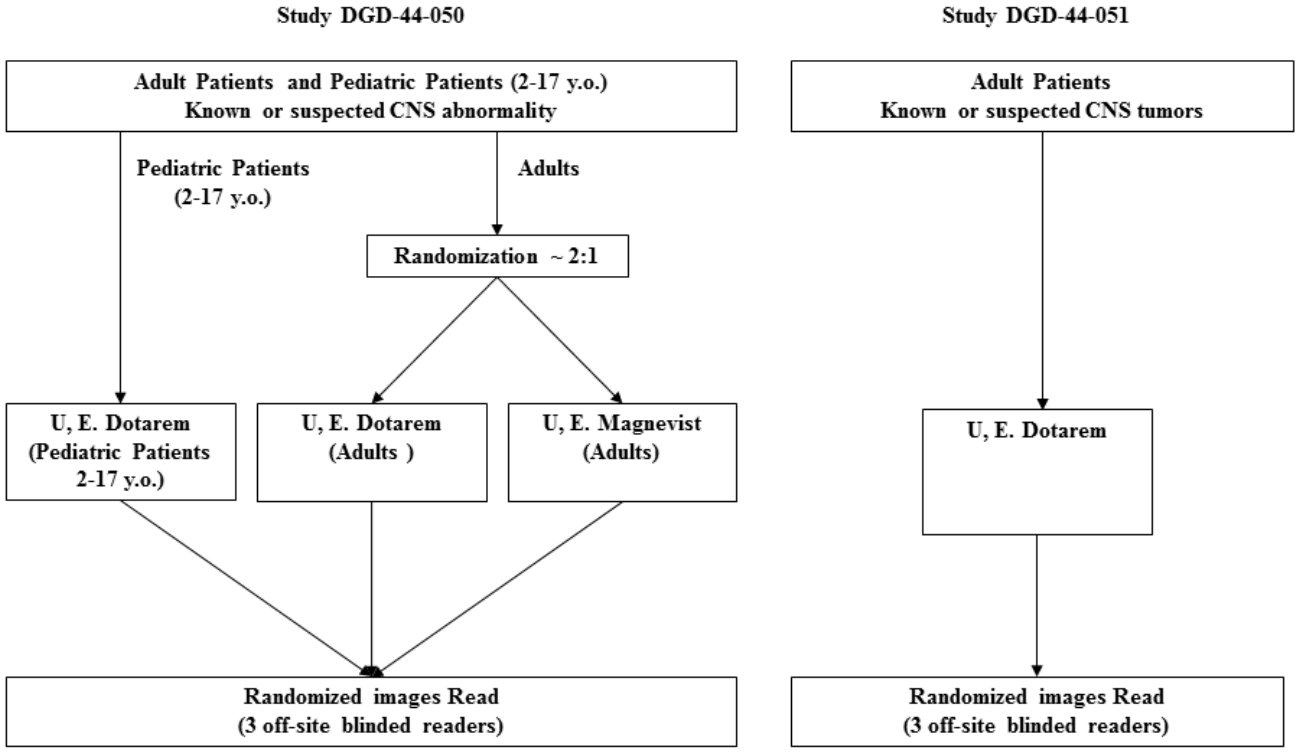
As primary efficacy analysis, it was agreed with FDA to compare the performance of Dotarem-enhanced MRI to that of unenhanced MRI, using 3 visualization endpoints as co-primary endpoints and demonstrate a superiority of Dotarem-enhanced MRI over unenhanced MRI (Figure 8). Statistically significant superiority in lesion visualization on "Paired" images (unenhanced plus Dotarem-enhanced MRI) over "Pre" images (unenhanced MRI) was to be demonstrated in at least 2 out of 3 readers for all three co-primary endpoints: lesion border delineation, lesion internal morphology and lesion contrast enhancement.

The FDA also agreed to use a comparator arm (Magnevist) to provide confirmation of validity of scoring and interpretation methodology and agreed to consider the comparison between Dotarem and Magnevist solely as part of the secondary efficacy analysis. Magnevist was selected as the positive control because it has a CNS indication approved in the US and it is the most used contrast agent in the US.

As part of the secondary analyses, the FDA also agreed with the assessment of the efficacy co-primary endpoints in an open-label arm of at least 30 pediatric patients, with a reasonable representation of age groups from 2 to 17 years of age. Furthermore, it was found unnecessary to expose pediatric patients to the comparator product.

The same primary efficacy analyses using the same co-primary endpoints were applied to study DGD-44-051 (re-read of previous DGD-3-44 study).

Figure 8: Pivotal Phase III Study Design



Abbreviations: U: Unenhanced (Pre-contrast); E: Enhanced (post-contrast)

8.3.2.1 MRI Images Acquisition

The study sites of both pivotal phase III studies were instructed to consistently perform MRI examination using predefined acquisition parameters for all patients included at each site. The following imaging sequences were required for study DGD-44-050:

Brain (Intracranial) Lesions: Mandatory Sequences:

- PRE contrast images (unenhanced MRI):
  - T1-weighted axial
  - T2-weighted axial
  - FLAIR axial
- POST contrast images (contrast-enhanced MRI):
  - T1-weighted axial

Spine Lesions: Mandatory Sequences:

- PRE contrast images (unenhanced MRI):
  - T1-weighted sagittal

- T2-weighted sagittal
- T1-weighted axial
- T2-weighted axial

o POST contrast images (contrast-enhanced MRI):

- T1-weighted sagittal
- T1-weighted axial

The study DGD-3-44 used similar imaging acquisition sequences but with additional orientations of images (coronal and sagittal for brain; coronal for spine).

8.3.2.2 Prospective Blinded Image Reading

8.3.2.2.1 Definitions

For each study, three experienced neuroradiologists were selected and trained for the independent reader role. Readers of study DGD-44-050 were different from and independent from readers of study DGD-44-051. No changes in readers occurred during the course of the assessments.

The complete imaging database was read by independent and fully blinded readers. In this context, the term "**independent**" means that the readers involved in centralized review did not participate in image acquisition and that images were read outside the image acquisition site. Moreover, no communication on reading findings was allowed between independent readers.

To ensure that the centralized reading evaluations remained independent, each individual reader evaluation was locked as they occurred (i.e. no further possibility to alter the evaluation). Furthermore, the readers did not have the possibility to search and view images from batches previously assessed.

The term "**blinded**" means that the readers did not have any knowledge of the following information:

- Patient-specific information (including name, identifiers, medical history, clinical examination, laboratory results, etc.).
- Name of institution where MR images were produced.
- Patient enrolment information (including inclusion and non-inclusion criteria).
- Results of any imaging examination other than the imaging examination to be read.
- Findings of any other readers (e.g., investigators, on-site readers and other central readers).
- Data related to the nature of the contrast medium.
- Nature of images in each reading set, other than information apparent from the aspect of the images themselves.

- Final diagnosis and patient outcome.

8.3.2.2.2 Preparation and Presentation of Images to Blinded Readers

The images received from sites were entered in a central database and accumulated into three different sets per patient by the imaging core lab:

- Set “Pre”: MR images without contrast agent administration (Pre contrast MRI)
- Set “Paired”: combined unenhanced and contrast-enhanced MRI (Pre+Post contrast MRI)
- Set “Post”: MR images after contrast agent administration (Post contrast MRI)

For the assessment of the co-primary evaluation criteria, sets “Pre” and sets “Paired” were analyzed. Sets “Post” were used only for analyses of some secondary evaluation criteria.

All images were de-identified to ensure reading in blind conditions.

Every batch of images (“Pre”, “Paired” and “Post” sets) available for 20 to 40 patients was randomized and presented to the three independent readers. A wash-out period of at least two weeks between the evaluations of 2 different sets for a single patient was ensured to minimize recall bias. In addition, the order of presentation of different sets to the readers was randomly determined for each batch of images.

8.3.2.3 Selection of the Study Population for the Phase III Studies

For both Phase III studies, the inclusion and non-inclusion criteria were designed to best reflect the population of patients who would be likely to benefit from a CE-MRI of the CNS in routine clinical practice. Patients were eligible for inclusion if:

- they were referred for CE-MRI of the CNS (brain, spine or associated tissues) based on previously completed diagnostic examinations,
- they were known or highly suspected of having pathologies of the CNS.

8.3.2.4 Analysis of Lesion Visualization Co-Primary Endpoints

The primary statistical assessment is based on the comparison of the “Pre” (unenhanced) versus the “Paired” (unenhanced + enhanced) images within the Dotarem treatment group. The 3 co-primary efficacy variables were focused on lesion visualization (lesion border delineation, internal morphology and degree of contrast enhancement) in “Pre” (unenhanced) versus “Paired” (unenhanced + enhanced) images of each patient.

Each image reader reviewed all images from “Pre” and “Paired” MRI modalities and rated each lesion up to a limit of the 5 largest representative lesions identified, employing a 3-point scale: unevaluable (0), seen but imperfectly (1) or seen completely/perfectly (2).

For each co-primary variable, the analyses were conducted according to the following steps:

- Patient scores: sum of all lesion scores for “Paired” and “Pre” assessments, giving a patient “paired” score and a patient “pre” score respectively.
- Mean scores of co-primary variable: mean of all patients “Paired” scores and mean of all patients “Pre” scores.

- Difference between the mean "Paired" score and the mean "Pre" score. As recommended by the FDA, for the patient score (first step above), the sum of lesions' scores was used instead of mean of lesions' scores within individual patients, in order to reflect the number of lesions detected.
- The efficacy of Dotarem was expected to be demonstrated for at least 2 out of 3 readers independently meeting a statistically significant positive difference between the mean "Paired" score and the mean "Pre" score for each co-primary endpoint (lesion border delineation, internal morphology and degree of contrast enhancement).

These study designs and analysis of "Paired" images compared to "Pre" images enabled to assess the superiority of contrast-enhanced MRI versus unenhanced MRI.

8.3.3 Results of Pivotal Phase III Studies

The two pivotal phase III studies focused on three co-primary endpoints: lesion border delineation, internal morphology and contrast enhancement. Both studies achieved the objective of superiority in visualization of "Paired" images (unenhanced + Dotarem-enhanced MRI) over "Pre" images (unenhanced MRI) for all three co-primary endpoints across all three readers.

The use of Magnevist group also provided confirmation of validity of scoring and interpretation method used to evaluate Dotarem efficacy.

8.3.3.1 Patient Disposition

A combined total of 428 patients received Dotarem in the 2 pivotal phase III studies.

Demographic data for the 2 pivotal studies are presented:

- in Table 8 for adult patients from DGD-44-050 study,
- in Table 9 for pediatric patients from DGD-44-050 study,
- in Table 10 for adult patients from DGD-3-44 study.

Study DGD-44-050 enrolled a somewhat greater number of female than male adult patients. The age range for the entire adult population was 18 to 94 years. The majority of patients were Caucasian (84.5% for Dotarem and 79.8% for Magnevist). A total of 22 female and 16 male pediatric patients, ranging in age from 2.9 to 17.3 years, participated in the study. The majority of pediatric patients (68.4%) were Caucasian.

In Study DGD-44-051 (the blinded image re-reading of DGD-3-44 MRI scans), there were more male than female patients and a slightly narrower age range, 18 to 79 years. The majority of patients were Caucasian (97.4%).

Table 8: Patient Demographics in Study DGD-44-050 (Adults) – FAS

Characteristic	Dotarem	Magnevist
Gender, N (%)		
Male	114 (46.5%)	54 (45.4%)
Female	131 (53.5%)	65 (54.6%)
Age (year)		
N	245	119
Mean (SD)	53.17 (14.35)	55.95 (14.43)
Median	55.10	57.40
Min., Max	18.80, 85.10	19.00, 94.40
Ethnicity, N (%)		
Caucasian	207 (84.5%)	95 (79.8%)
Asian	27 (11.0%)	15 (12.6%)
Black	9 (3.7%)	8 (6.7%)
Other	2 (0.8%)	1 (0.8%)
Height (cm)		
N	242	119
Mean (SD)	168.26 (9.89)	167.34 (9.77)
Median	168.00	168.00
Min., Max	138.00, 194.00	146.00, 196.00
Weight (kg)		
N	244	118
Mean (SD)	76.04 (17.03)	76.70 (16.44)
Median	74.00	75.00
Min., Max	43.00, 136.00	44.00, 135.40
Body Mass Index (kg/m^2)		
N	241	118
Mean (SD)	26.82 (5.32)	27.30 (4.89)
Median	26.08	26.84
Min., Max	16.65, 51.30	16.56, 47.27

Abbreviations: FAS = Full Analysis Set; Max = maximum value; Min = minimum value;
SD = standard deviation

Table 9: Patient Demographics in Study DGD-44-050 (Pediatric Patients) - FAS

Characteristic	**Dotarem (N = 38)**
Gender, N (%)	
Male	16 (42.1%)
Female	22 (57.9%)
Age (years)	
Mean (SD)	9.29 (4.49)
Median	7.65
Min, Max	2.90, 17.30
Ethnicity, N (%)	
Caucasian	26 (68.4%)
Black	9 (23.7%)
Other	3 (7.9%)
Height (cm)	
Mean (SD)	133.84 (23.85)
Median	128.50
Min, Max	98.0, 177.0
Weight (kg)	
Mean (SD)	36.01 (19.72)
Median	29.00
Min, Max	13.00, 87.00
Body Mass Index (kg/m^2)	
Mean (SD)	18.55 (4.23)
Median	17.42
Min, Max	12.50, 29.73

Abbreviations: Max = maximum value; Min = minimum value; SD = standard deviation

Table 10: Patient Demographics in Study DGD-44-051, FAS

Characteristic	Dotarem
Gender, N (%)	
Male	84 (55.6%)
Female	67 (44.4%)
Age (year)	
N	151
Mean (SD)	53.9 (13.5)
Median	55.0
Min, Max	18.0, 79.0
Ethnicity, N (%)	
Caucasian	147 (97.4%)
Black	1 (0.7%)
Other	3 (2.0%)
Height (cm)	
N	136
Mean (SD)	169.8 (9.1)
Median	170.0
Min, Max	141.0, 197.0
Weight (kg)	
N	151
Mean (SD)	73.2 (13.8)
Median	72.0
Min, Max	41.0, 120.0
Body Mass Index (kg /m^2)	
N	136
Mean (SD)	25.6 (4.0)
Median	25.1
Min, Max	16.9 – 39.2

Abbreviations: Max = maximum value; Min = minimum value; SD = standard deviation

8.3.3.2 Lesion Visualization Co-Primary Endpoints for Both Phase III Pivotal Studies in Adult patients

Results for lesion visualization co-primary endpoints (border delineation, internal morphology and contrast enhancement) are summarized in Table 11 for adult patients, respectively. For both Phase III studies, Dotarem-enhanced images were shown to be superior over unenhanced images for all 3 off-site blinded readers. This superiority was statistically significant in adults ($p<0.001$) for both studies (Table 11).

Table 11: Lesion Visualization Endpoint Results in Adults with Dotarem in Both Phase III Studies (Patient Level) - FAS

	Study DGD-44-050						Study DGD-44-051					
Readers	**R1**		**R2**		**R3**		**R1**		**R2**		**R3**	
Modality	**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**
N Patients	**224**	**230**	**224**	**230**	**222**	**235**	**149**	**149**	**149**	**149**	**149**	**149**
Border Delineation												
Mean score (SD)	1.06 (1.23)	3.30 (2.64)	1.62 (1.43)	4.49 (2.94)	1.43 (1.29)	2.54 (2.30)	0.94 (0.07)	1.98 ((0.07)	1.41 (0.08)	2.18 (0.08)	0.34 (0.08)	1.62 (0.08)
Difference*	2.26		2.92		1.15		1.05		0.77		1.28	
Internal Morphology												
Mean score (SD)	0.97 (1.05)	3.70 (2.63)	1.76 (1.24)	4.49 (2.93)	1.45 (1.13)	2.93 (2.30)	1.09 (0.07)	2.23 (0.07)	1.34 (0.08)	2.28 (0.08)	0.67 (0.08)	2.41 (0.08)
Difference*	2.75		2.77		1.54		1.14		0.94		1.74	
Contrast Enhancement												
Mean score (SD)	0.01 (0.20)	3.11 (2.52)	0.01 (0.15)	3.73 (2.67)	0.01 (0.13)	2.95 (2.44)	0.00 (0.06)	2.06 (0.06)	0.00 (0.07)	2.11 (0.07)	0.00 (0.07)	2.21 (0.07)
Difference*	3.13		3.76		2.99		2.06		2.10		2.21	

Abbreviations: Paired = MRI scans obtained before and after Dotarem administration; Pre = before Dotarem administration; SD = Standard Deviation

* Difference = "Paired" mean – "Pre" mean. All differences are statistically significant ($p<0.001$). Differences are calculated based on patients with both "Pre" and "Paired" scores available.

8.3.3.3 Lesion Visualization Results for Magnevist and the Comparison Between Dotarem and Magnevist in Adults (Study DGD-44-050)

One of the secondary analyses in Study DGD-44-050 was to evaluate the use of Magnevist as a measure of validation for the study. This involved the assessment of the same "Paired" (unenhanced plus enhanced) versus "Pre" (unenhanced) images for the 3 co-primary variables. The mean differences in lesion visualization scores between "Paired" and "Pre" modalities with Magnevist were similar to those obtained with Dotarem. Thus, the comparison between Dotarem and Magnevist showed no significant differences between the 2 contrast agents for all 3 co-primary variables with the 3 off-site blinded readers.

8.3.3.4 Lesion Visualization Co-Primary Endpoints: Stratified by Gender, Ethnicity and Geographic Region for Study DGD-44-050

Stratification of the data for each of the co-primary endpoints was consistent across gender, ethnicity and geographic region. There were no clinically relevant differences in efficacy based on gender, ethnicity or geographic regions.

8.4 Supportive Studies in CNS Indication in Adults

The efficacy of Dotarem-enhanced MRI in the CNS indication was further supported by 2 additional double-blind, randomized, positive-control clinical studies (DGD-3-17 and DGD-3-31). Study DGD-3-17 showed that administration of Dotarem provided substantial diagnostic value, comparable to Magnevist, over non-enhanced MRI images in a small study of 20 adult patients. It was also comparable to Magnevist in a larger study involving 298 adult patients (DGD-3-31).

Furthermore, there were 16 open-label, non-randomized, single-group investigations involving 643 adult patients evaluated for CNS lesions. These studies demonstrated the administration of Dotarem in MRI provided a good to excellent contribution to the diagnostic assessment of the individual patient. Dotarem was found to contribute to a change in the diagnostic evaluation and a modification of the therapeutic management in a majority of the patients.

8.5 Pivotal Phase III Studies in CNS Indication in Pediatric Patients

Table 12 presents lesion visualization data for each of the 3 co-primary variables for the pediatric population. For all 3 readers, mean scores for each endpoint were higher for "Paired" relative to "Pre" mean scores according to descriptive statistics.

Table 12: Lesion Visualization Endpoint Results in Pediatric Patients with Dotarem in Phase III Study DGD-44-050 (Patient Level) - FAS

		Off-site					
Readers		**Reader 1**		**Reader 2**		**Reader 3**	
Modality		**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**
N Patients		**31**	**32**	**34**	**35**	**33**	**36**
Border Delineation	Mean scores (SD)	1.42 (1.09)	2.47 (1.52)	1.18 (1.03)	3.51 (2.50)	1.06 (0.66)	1.36 (1.10)
Internal Morphology	Mean scores (SD)	1.13 (0.88)	2.75 (1.50)	1.41 (0.78)	3.51 (2.48)	1.06 (0.56)	1.81 (1.09)
Contrast Enhancement	Mean scores (SD)	0	1.81 (1.09)	0	2.69 (2.03)	0	1.64 (1.25)

Abbreviations: Paired = MRI scans obtained before and after Dotarem administration; Pre = before Dotarem administration; SD = standard deviation

8.6 Supportive Studies in CNS Indication in Pediatric Patients

Three non-randomized, single-group Dotarem studies that collectively enrolled a total of 99 pediatric patients, ages 1.2 months to 17 years, were conducted by Guerbet between 1988 and 1991. Patients received Dotarem at a dose of 0.1 mmol/kg intravenously. The results of these studies showed that Dotarem-enhanced MRI was complementary or superior to unenhanced MRI for lesion detection and/or characterization.

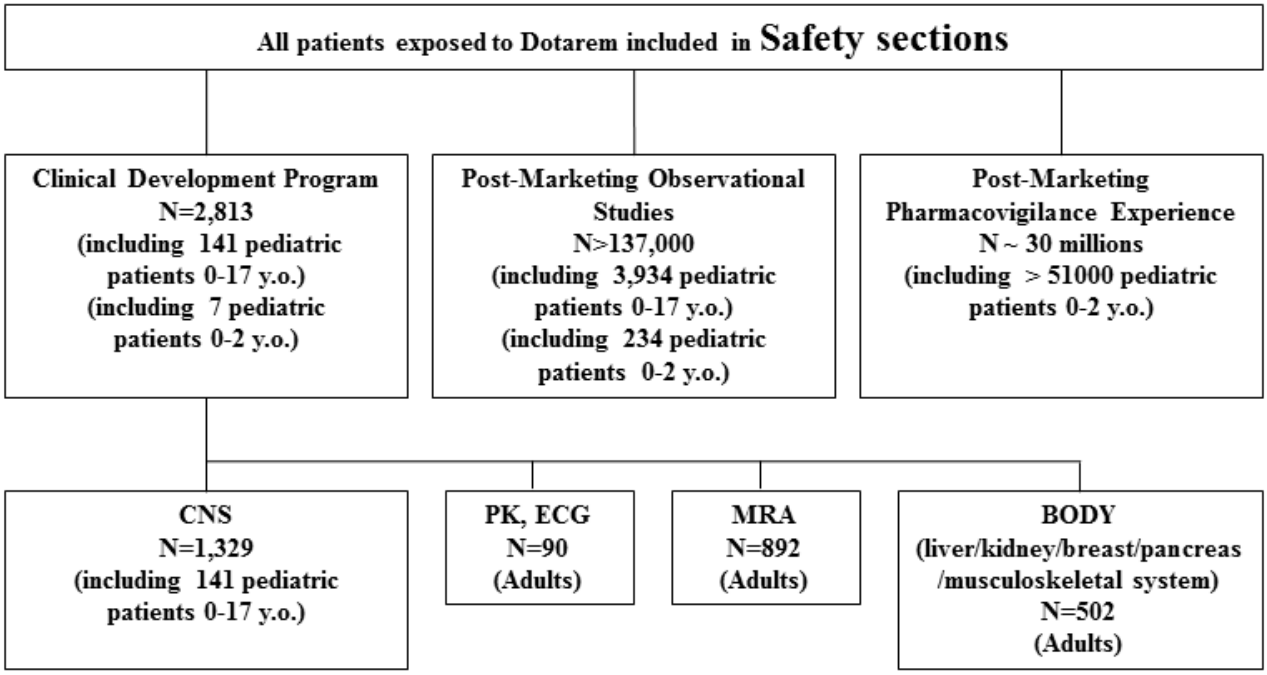
9 SAFETY

Summary:

- The clinical safety profile of Dotarem has been well characterized during a large clinical development program (49 clinical studies including 2813 adults and pediatric patients who received Dotarem).
- The most frequently reported related AE were nausea, headache and injection site pain.
- 29 SAEs (including fatalities) were observed in 23 (0.8%) patients treated with Dotarem. Among SAEs in Dotarem-treated patients, 2 were considered to be possibly related to treatment (moderate hypersensitivity and mild increase in serum creatinine) and none of them were fatal.
- Six post-marketing observational studies with more than 137,000 patients provide reassuring additional safety data for both adult and pediatric populations
- Accumulated post-marketing safety data, based on approximately 30 million doses, demonstrated a well-characterized safety profile consistent with the AEs observed in clinical studies. Most reactions were reported in the system organ classes of Skin and subcutaneous tissue disorders (26.9%), Gastrointestinal disorders (18.4%) and Respiratory, thoracic and mediastinal disorders (13.7%).
- Based on the clinical studies and supported by the results of the post-marketing observational studies, Dotarem was well tolerated in pediatric patients, including those less than 2 years of age. Accumulated safety data in children do not differ from what is currently known in the adult population.
- No cases of NSF or NSF-like symptoms have been observed in clinical studies. No single-agent/unconfounded cases of NSF were reported for Dotarem in the post-marketing experience, according to an assessment based on available clinical and histological information (Girardi *et al.*, 2011).

Figure 9 provides patients distribution for safety assessment of Dotarem through clinical studies, post marketing observational studies and post marketing experience.

Figure 9: Breakdown of All Patients Exposed to Dotarem Included in Safety Sections



A specific analysis of safety in pediatric patients less than 2 years of age is provided in Section 11.

9.1 Clinical Studies

Safety data were derived from 49 clinical studies (3 Phase I pharmacokinetic studies, one thorough QT study and 45 Phase II-IV studies) conducted for various imaging purposes from 1987 to 2011.

Clinical safety was assessed in all studies. Among them:

- One study specifically evaluated ECGs and QT interval after Dotarem injection.
- 17 studies included data on blood pressure and heart rate monitoring.
- 21 studies included extensive laboratory evaluations before and after Dotarem injection.

The total safety population from clinical studies included 2813 patients (2672 adults, 141 pediatric patients aged 0-17 years) who received at least one dose of Dotarem.

A comparator contrast media agent (i.e. Magnevist or Gadavist) was administered to 371 patients in 5 studies (3 CNS and 2 MRA).

The safety data include patients with adverse events (AEs) following study product administration, clinical laboratory assays, vital signs, physical examinations and electrocardiography evaluations.

9.1.1 Methods for Safety Analysis

Analyses of safety are based on 49 clinical studies performed in various indications (Appendix 2). Analyses were conducted according to a statistical analysis plan using pooled data from these clinical studies.

Treatment groups were defined as:

- Dotarem: patients exposed to Dotarem (2813 patients).
- Magnevist or other GBCAs: patients exposed to Magnevist (276 patients) or Gadavist (95 patients).

For the pooled dataset, analyses were conducted by treatment group for the overall population as well as for subpopulations as noted below:

- Patient demographics (race, gender, age, weight, height)
- Past or current pathologies at inclusion
- Allergy history
- Concomitant treatment at inclusion
- Product administration characteristics
- AEs (including related AEs and non-related AEs)
- AEs leading to death
- Treatments for AEs
- SAEs
- Withdrawals from study

9.1.2 Exposure to the Drug

As a diagnostic agent, Dotarem is usually administered at the standard single dose of 0.1 mmol/kg BW in a single bolus IV injection.

Based on all 49 clinical studies:

- The mean dose of Dotarem administered was 0.1 mmol/kg BW (0.2 mL/kg BW). Most patients received doses between 0.05 and 0.1 mmol/kg BW (66.4%).
- The mean volume of injection was 16.3 mL.
- The mean rate of injection was 1.7 mL/sec.

9.1.3 Adverse Events

Based on the clinical safety database (N= 2813 patients), most patients treated with Dotarem (90.4%) did not experience AEs. Of the 263 patients (9.3%) treated with Dotarem who did experience AEs, 111 (3.9%) had AEs that were considered to be related to Dotarem (Table 13).

Table 13: Patients with AEs

	Product Administration	
	Dotarem N = 2813	**Magnevist or other GBCA N = 371**
Patients With at least one AEs		
Information missing	6 (0.2%)	0
No	2544 (90.4%)	320 (86.3%)
Yes	263 (9.3%)	51 (13.7%)
Patients with AE by relationship to treatment		
Unknown	22 (0.8 %)	0
Not related AEs	130 (4.6%)	15 (4.0%)
Related AEs	111 (3.9%)	36 (9.7%)

Abbreviations: AE= adverse event

Most AEs were mild (71.1%) and the majority (72.5%) resolved without treatment.

The most common related AEs in Dotarem-treated patients were nausea (0.6%), headache (0.5%) and injection site pain (0.4%) (Table 14). All other related AEs occurred in < 0.2% of patients.

Table 14: Related Adverse Events ≥ 0.2% of Dotarem-Treated Patients

System Organ Class Preferred Term	Product Administration	
	Dotarem N = 2813	**Magnevist or other GBCA N = 371**
Nausea	18 (0.6%)	4 (1.1%)
Headache	13 (0.5%)	16 (4.3%)
Injection site pain	11 (0.4%)	5 (1.3%)
Injection site coldness	6 (0.2%)	1 (0.3%)
Feeling hot	5 (0.2%)	3 (0.8%)
Burning sensation	5 (0.2%)	0

Note: An adverse event encountered several times in 1 patient was counted once; the same rule applied for preferred terms and system organ classification. Adverse events are listed by order of decreasing incidence first in the Dotarem-treated group, then in the Magnevist or other GBCA group, and then alphabetically for those with the same incidence.

No particular risk emerged from any system organ class.

9.1.3.1 Analysis by Dose

In the 49 clinical studies, no relationship with the injected dose of Dotarem was apparent (Table 15).

Table 15: Summary of AEs by Dose of Contrast Agent (All Studies)

Parameters	Product Administration					
	>0 to <0.05 mmol/kg		0.05 to 0.1 mmol/kg		>0.1 mmol/kg	
	Dotarem N = 5	Magnevist or other GBCA N = 80	Dotarem N = 1868	Magnevist or other GBCA N = 237	Dotarem N = 934	Magnevist or other GBCA N = 54
Patients with at least one AE						
A	0	0	6	0	0	0
No	3 (60.0%)	78 (97.5%)	1681 (90.0%)	201 (84.8%)	854 (91.4%)	41 (75.9%)
Yes	2 (40.0%)	2 (2.5%)	181 (9.7%)	36 (15.2%)	80 (8.6%)	13 (24.1%)
Patients with AEs by relationship to treatment						
Unknown	0	0	19	0	3	0
Non-related AEs	2 (40.0%)	1 (1.3%)	93 (5.0%)	12 (5.1%)	35 (3.8%)	2 (3.7%)
Related AEs	0	1 (1.3%)	69 (3.7%)	24 (10.1%)	42 (4.5%)	11 (20.4%)

Abbreviations: A = information not requested in study; AE = adverse event

The 3 most common AEs were similar between the total population who received Dotarem and the population sorted by dose. Injection site reactions were rare (<1%), regardless of the Dotarem dose administered.

9.1.3.2 Analysis by Age, Gender and Race

Patients ranged in age from 0.1 to 97 years of age with a mean of 53.7 years. Among adults who received Dotarem, the incidence of related AEs ranged between 2.7% to 4.5%. Analyses of AEs based on age revealed no significant differences in incidence rates or severity. Pediatric safety is discussed in Section 9.2.

Of the 2813 patients, 1532 (54.5%) were male patients. The incidence of related AEs was 4.8% in female patients and 3.3% in male patients. Analyses of AEs based on gender revealed no significant differences in incidence rates or severity.

Most patients who received Dotarem were Caucasian patients (1181 patients [74.4%]), followed by Asian (11.9%), Black (4.0%) and Other (9.6%) patients. The incidence of related AEs was 5.0% in Caucasian patients, 6.3% in Black patients and 2.1% in Asian patients. Analyses of AEs based on race revealed no significant differences in severity.

No particular subgroup based on age, gender or race appeared to be at an increased risk of adverse effects of drug treatment.

9.1.4 Serious Adverse Events

During the overall clinical development, SAEs were observed in 23 (0.8 %) of 2813 patients treated with Dotarem representing 29 SAEs. Among them, 8 patients treated with Dotarem had a fatal outcome, but none were considered related to treatment (see Section 9.1.5). Seven of these patients were included in study DGD-3-44 assessing Dotarem efficacy and safety in patients with progressive CNS tumors.

Among 15 patients with other non-fatal SAEs, 6 required hospitalization or prolongation of hospital stay and 4 experienced an immediately life-threatening event. Among non-fatal SAEs in Dotarem-treated patients, 2 were considered to be possibly related to treatment: there was an event of hypersensitivity of moderate intensity in a male patient and an event of mild increase in serum creatinine in a female patient with a medical history of moderate chronic renal failure. Most of the SAEs occurred at a dose of 0.1 mmol/kg and 2 SAEs occurred before administration of Dotarem.

Six patients recovered after treatment for their SAEs, 8 recovered without treatment, one recovered with sequelae and one patient presenting with 2 SAEs had not recovered from one of the SAEs (the other one resolved).

During clinical development of Dotarem, no cases of NSF or NSF-like symptoms have been reported. Post-marketing information of NSF reports is provided in Section 10.

9.1.5 Deaths During Clinical Studies

Eight deaths were recorded in clinical studies conducted by Guerbet, all of which were not related to Dotarem (Table 16).

- Seven deaths were reported in Phase III Study DGD-3-44, which involved evaluation of MRI with Dotarem in the diagnosis or follow-up assessment of cerebral or spinal tumors.
- One death occurred in Phase III Study DGD-3-50, which involved evaluation of MRI with Dotarem in the characterization of abdominal and pelvic lesions.

Table 16: Deaths in Clinical Studies

Treatment/ Study	Subject	Gender/ Age	Preferred Term	Relationship to Contrast Agent	Intensity	SAE	Outcome
Dotarem							
DGD-3-44†	01017	Female 40	Cerebral ischaemia	Not related	Severe	Yes	Death
	02012	Male 52	Cerebral haemorrhage‡	Not related	Severe	Yes	Death
			Thrombophlebitis	Not related	Severe	Yes	Death
	03029	Female 55	Condition Aggravated	Not related	Severe	No*	Death
			Metastatic neoplasm	Not related	Severe	Yes	Death
	06001	Male 64	Cardiac failure	Not related	Severe	Yes	Death
	06005	Male 47	Pulmonary embolism	Not related	Severe	Yes	Death
	08005	Male 71	Intracranial pressure increased	Not related	Severe	Yes	Death
	10001	Female 18	Post procedural haemorrhage	Not related	Severe	Yes	Death
			Vasospasm	Not related	Severe	Yes	Death
DGD-3-50	05001	Male 76	Cardiac failure	Not related	Severe	Yes	Death

† Study involving MRI of CNS

* The event was not considered as serious by the investigator. However, the final outcome being death, seriousness at case level was considered serious.

‡ Considers as one SAE the duplicate coding brain hemorrhage for Patient 02012 in Study DGD-3-44, which was coded to both CEREBRAL HEMORRHAGE and HEMORRHAGE MedDRA preferred terms.

9.1.6 Clinical Laboratory Evaluations and Vital Signs

Clinical laboratory evaluations (hematology and/or biochemistry) were described in 21 studies, including pharmacokinetic and pediatric studies involving a total of 1092 patients treated with Dotarem. No remarkable changes from baseline were observed for these parameters (Appendix 3).

Vital signs were assessed in the 2 pivotal studies and in 15 other supportive studies on a total number of 1547 patients. No clinically significant effects were observed for vital signs (blood pressure, heart rate, respiratory rate) following Dotarem injection. The mean values showed minimal fluctuations from pre-procedure at each time point post injection (Appendix 3). The changes observed in vital sign parameters were attributed to underlying conditions or procedure-related stress, which is expected with this type of MRI examination.

9.1.7 ECG Safety Studies

9.1.7.1 Thorough QT Study

The thorough QT Study (DGD-44-039) involved 40 patients who received a cumulative 0.3 mmol/kg dose of Dotarem, and 11 ECGs were performed for each subject for each period. The cumulative dose of 0.3 mmol/kg was chosen as this dose corresponded to the highest dose used in clinical practice, thereby providing an appropriate pharmacological setting to investigate the effect of Dotarem on QT interval. Forty patients were included in the study and randomized to receive Dotarem and placebo in either sequence order. There were no clinically significant abnormalities in the laboratory safety and vital sign results. ECG parameter analyses showed that Dotarem had no effect on QT, QTc interval or other ECG parameters after bolus IV administration at the highest cumulative dose of 0.3 mmol/kg.

9.1.7.2 ECG in Clinical Studies

ECG parameters of Dotarem were evaluated in 50 patients during 3 controlled clinical studies (DGD-3-6, DGD-3-28, DGD-3-48) performed by Guerbet. No abnormalities were observed.

For pivotal Study DGD-44-050, ECGs were performed in a subset of 91 adult patients (63 Dotarem, 28 Magnevist) and 12 pediatric patients treated with Dotarem at baseline. ECG parameters were collected prior to CE-MRI and 30 minutes post injection. A small and equivalent increase in mean QTc (both Fridericia and Bazett) was observed with both Dotarem and Magnevist in adult and pediatric patients when comparing baseline ECG analyses to analyses at 30 minutes post injection (mean change of QTc Fridericia from baseline, 30 min after injection, was 7.25 msec for Dotarem and 10.32 msec for Magnevist).

9.2 Safety for Pediatric Patients in Clinical Studies

The pediatric population consisted of 137 patients included in 4 clinical studies: 3 pediatric studies (DGD-3-15, DGD-3-16 and DGD-3-29) and one pivotal study (DGD-44-050). In addition, 4 pediatric patients (12-17 years of age) were inadvertently included in 3 other clinical studies conducted in adults. All 7 studies were designed to evaluate MRI of the CNS. For safety, the pediatric population consisted of 141 pediatric patients (Table 17).

Table 17: Disposition of Pediatric Patients

Study No.	Number of Pediatric Patients
DGD 3-04	1
DGD 3-05	1
DGD 3-21	2
DGD 3-15	29
DGD 3-16	20
DGD 3-29	50
DGD-44-050	38
Total	**141**

Seven patients aged 1 to <24 months, 33 aged 2 to <6 years, 58 aged 6 to <12 years and 43 aged 12 to 17 years, received Dotarem. The mean dose of Dotarem in all age groups was 0.1 mmol/kg. The mean volume of injection in pediatric patients progressively increased with age; it was 1.6 mL in patients aged 1 to <24 months, 3.3 mL in patients aged 2 to <6 years, 5.8 mL in patients aged 6 to <12 years and 10.4 mL in patients aged 12 to 17 years (Table 18).

Table 18: Product Administration Characteristics by Age at Inclusion (1 Month to 17 Years) (All Studies)

	Age/Product Administration				
	1 to <24 Months†	2 to <6 Years†	6 to <12 Years†	12 to 17 Years	
Parameter	Dotarem N = 7	Dotarem N = 33	Dotarem N = 58	Dotarem N = 43	Magnevist or other GBCA N = 1
Volume actually administered (mL)					
Mean (SD)	1.6 (0.5)	3.3 (1.0)	5.8 (1.8)	10.4 (2.9)	13.0 (-)
Median	1.9	3.0	5.7	10.4	13.0
Min, Max	0.6/2.0	2.2/6.5	2.4/13.2	6.0/17.4	13.0/13.0
Dose (mmol/kg)					
Mean (SD)	0.1 (0)	0.1 (0.05)	0.1 (0.0)	0.1 (0)	0.1 (-)
Median	0.1	0.1	0.1	0.1	0.1
Min, Max	0.1/0.1	0.1/0.25	0.1/0.2	0.1/0.1	0.1/0.1

Abbreviations: - = not applicable; Max = maximum value; Min = minimum value; SD = standard deviation
†No patients aged 1 to <24 months, 2 to <6 years, or 6 to <12 years received Magnevist or other GBCA.

Among pediatric patients who received Dotarem, the incidence of AEs ranged between 4.7% and 14.3%. No patients in the youngest age group (1 to <24 months) had AEs related to Dotarem treatment; one in the 2 to <6 year age group, 4 in the 6 to <12 year age group and one in the 12 to 17 year age group had related AEs (Table 19).

Table 19: AEs by Age at Inclusion (1 Month to 17 Years) (All Studies)

	Age/Product Administration				
	1 to <24 Months†	2 to <6 Years†	6 to <12 Years†	12 to 17 Years	
Parameter	Dotarem N = 7	Dotarem N = 33	Dotarem N = 58	Dotarem N = 43	Magnevist or other GBCA N = 1
Patients with at least 1 AE					
No	6 (85.7%)	31 (93.9%)	52 (89.7%)	41 (95.3%)	1 (100%)
Yes	1 (14.3%)	2 (6.1%)	6 (10.3%)	2 (4.7%)	0
Patients with adverse events by relationship to treatment					
Nonrelated AEs	1 (14.3%)	1 (3.0%)	2 (3.5%)	1 (2.3%)	0
Related AEs	0	1 (3.0%)	4 (6.9%)	1 (2.3%)	0

Abbreviations: AE = adverse event
† No patients aged 1 to <24 months, 2 to <6 years, or 6 to <12 years received Magnevist or other GBCA.

Related AEs with an incidence ≥0.2% in Dotarem-treated pediatric patients included headache, pruritus, asthenia, injection site urticaria, nausea, dizziness, hematuria and vomiting (Table 20).

Table 20: Incidence of Related Adverse Events by Preferred Term in ≥0.2% of Dotarem-Treated Patients in Any Age Group by Age at Inclusion (1 Month to 17 Years) (All Studies)

	Age/Product Administration				
	1 to <24 Months†	2 to <6 years†	6 to <12 Years†	12 to 17 Years	
Preferred Term	Dotarem N = 7	Dotarem N = 33	Dotarem N = 58	Dotarem N = 43	Magnevist or other GBCA N = 1
Pruritus	0	1 (3.0%)	0	0	0
Headache	0	0	2 (3.4%)	0	0
Dizziness	0	0	1 (1.7%)	0	0
Hematuria	0	0	1 (1.7%)	0	0
Vomiting	0	0	1 (1.7%)	0	0
Asthenia	0	0	0	1 (2.3%)	0
Injection site urticaria	0	0	0	1 (2.3%)	0
Nausea	0	0	0	1 (2.3%)	0

† No patients aged 1 to <24 months, 2 to <6 years, or 6 to <12 years received Magnevist or other GBCA.
Note: An adverse event encountered several times in 1 patient was counted once; the same rule applied for preferred terms and system organ classification. Adverse events are listed first by incidence in the 1 to <24 months Dotarem-treated age group, then by incidence in the 2 to <6 years age group, then in the 6 to <12 years age group, then in the 12 to 17 year age group, then alphabetically.

9.2.1 Clinical Safety for Pediatric Patients from 2 to 17 Years of Age

Among the pediatric population from 2 years of age included in the clinical studies, there were 10 patients who experienced at least one AE, of which 6 patients had related AEs, all

considered non serious. They presented mainly with nausea/vomiting (3 cases), headaches (2 cases), dizziness, weakness, pruritus, injection site urticaria and hematuria (one case each), and all recovered without any specific treatment.

Only one non-related SAE has been reported in a 5 year-old patient with a medical history of CNS tumor; she received 4 mL of Dotarem (0.2 mL/kg) intravenously during an MRI for post-surgical control of CNS tumor. The day after, the patient experienced severe hypoxia due to abundant bronchial secretion obstructing the canula of the tracheostomy. Her condition was stabilized after the tracheostomy canula was changed. Some weeks later, the patient experienced worsening of chronic neurological damage and required respiratory assistance. She was moved to a respiratory unit. No specific measures have been taken. The patient's condition was stable. Both events were considered by the investigator as not related to Dotarem but more likely due to the underlying disease.

9.2.2 Summary of Safety in Pediatric Patients

No related AEs occurred in pediatric patients aged 1 to <24 months old. Among patients aged 2 to <6 years, pruritus in one patient was the only related AE reported. Headache in 2 patients and dizziness, hematuria and vomiting (each in one patient) were the only related AEs reported among patients 6 to <12 years old. Asthenia, injection site urticaria and nausea (each in one patient) were the only related AEs reported among patients 12 to <18 years old.

There was no evidence of an increased incidence of AEs among pediatric patients in CNS studies. The only related AE that occurred in more than one pediatric patient in CNS studies was headache, which occurred in 2 patients in the 2 to <6 year age group. Moreover, the incidence of AEs in pediatric patients and adults is comparable.

No NSF events were described in this study population.

Based on these clinical studies, Dotarem was well tolerated in pediatric patients. Accumulated safety data in children do not differ from what is currently observed in the adult population.

9.3 Post-Marketing Prospective Observational Studies

As previously mentioned, a total of 6 post-marketing prospective observational studies (Maurer *et al.*, 2012; Emond *et al.*, 2011; Ishiguchi *et al.*, 2010; Briand *et al.*, 1992; Neiss *et al.*, 1991, SECURE ongoing study) included more than 137,000 patients. These studies provide safety results in the CNS indication and are summarized below.

9.3.1 German PMS Study (Maurer *et al.*, 2012)

Among 104,033 patients enrolled in this post-marketing study, a total of 46,736 patients (44.9%) were men and 56,222 were women (54.0%). The gender of 1075 patients (1.0%) was not recorded. Their mean (SD) age was 52.2 years (16.9 years) (range: 5 weeks-97 years). Each patient was monitored for AEs during and for 30 to 60 minutes after the MR examination.

AEs occurred after injection of Dotarem in 328 out of 104,033 patients (0.3%). AEs were predominantly mild to moderate, and uncommon to very rare. A causal relationship was determined in 226 patients. A relationship with Dotarem was excluded in 2 out of 228 patients (0.9%).

The patients' outcome was provided in 224 patients: 217 of the 224 patients (96.9%) recovered after the examination, 2 patients (0.9%) had not yet recovered and the outcome was unknown in 5 patients (2.2%). In patients who had not yet recovered after the examination, AEs of pruritus, pustular rash and urticaria were observed.

Eleven patients presented with at least one SAE (0.01%). A positive causal relationship with Dotarem was assessed in 10 patients and not provided in one patient. Ten patients recovered after treatment of the AE, while the outcome was unknown in one patient.

There was an increased risk of AEs in patients with allergic predisposition and in patients with a previous reaction to contrast medium. No increased risk of AEs or of SAEs was demonstrated in patients with bronchial asthma who were given beta blockers simultaneously and in patients with cardiovascular diseases, renal insufficiency or CNS disorders.

AEs were observed in 0.3% of all patients (adult and pediatric patients). The study results demonstrate that Dotarem is a safe contrast medium for patients with and without risk factors, and facilitated diagnosis with optimal image quality.

9.3.2 French PMS Study (Emond *et al.*, 2011)

The aim of this study was to gain further knowledge on the safety of Dotarem during MRI in children less than 18 months of age during routine clinical practice.

A total of 104 neonates and infants (3 days-18 months) were enrolled from a single pediatric hospital in France.

The injected volume of Dotarem per patient ranged from 0.6 mL in a newborn (male, 3 days old, 3 kg) to 4 mL in the heaviest/oldest infant (female, 18 months, 20 kg), with a median of 2 mL, followed by the same volume of normal saline flush. The onsite follow up duration was 2h after Dotarem administration.

No AEs were reported by the investigator.

This post-marketing observational study showed no immediate adverse effects following IV administration of Dotarem in neonates and infants younger than 18 months of age undergoing MRI.

9.3.3 Japanese PMS Study (Ishiguchi *et al.*, 2010)

The aim of this study was to assess the safety of Dotarem in patients undergoing imaging of the brain/spinal cord and/or trunk/limbs, and to identify factors associated with the onset of adverse reactions; 3444 patients were included.

After administration of Dotarem, AE for outpatients were recorded up to at least 2h on-site and in-patients were followed-up for several days.

A total of 40 adverse reactions were recorded in 32 patients, with an overall incidence of 0.93%. Gastrointestinal disorders were the most commonly reported adverse reactions (0.49%). Most adverse reactions reported were of mild intensity and no serious adverse reactions were reported. This study found that statistically significant risk factors for adverse reactions were general patient condition, liver disorder, kidney disorder, health complications, concomitant treatments and Dotarem dose (although the incidence of adverse reactions was not dose dependent).

This post-marketing observational study showed a satisfactory safety profile for Dotarem.

9.3.4 French PMS Study (Briand *et al.*, 1992)

This post-marketing survey was conducted in France in a pediatric population of 402 patients. Overall, 81% of the pediatric patients were ≤15 years old and 6.5% were ≤2 years of age. A mean dose of 0.22 mL/kg was injected (range: 0.10-0.78 mL/kg).

The only AE reported was seen in a 16 year-old adolescent who developed a papule on the inside of the thigh 10 minutes after the injection, but this did not require discontinuation of treatment.

The results confirmed that Dotarem was well tolerated in pediatric patients.

9.3.5 European PMS Study (Neiss *et al.*, 1991)

The aim of this study was to assess the efficacy and safety of Dotarem in magnetic resonance examinations in 4169 patients that included 305 pediatric patients in 99 centers (France, Switzerland, and Belgium). Dotarem administered doses ranged from 0.15 to 0.25 mL/kg (i.e., 0.07-0.13 mmol/kg).

A total of 35 patients (0.84%) experienced at least one AE. The majority of the 43 AEs observed were considered as mild or moderate in intensity. The most frequent AEs reported were vomiting, nausea and headache. There were no SAEs.

The results confirm a satisfactory safety profile of Dotarem injection for MRI in adults and pediatric patients.

9.3.6 International PMS Study (SECURE Ongoing Study)

The aim of this worldwide ongoing observational post-marketing study is to obtain an international database of 40,000 patient examinations (adults and children) and to examine the general safety profile of Dotarem. Patients with or without renal insufficiency and undergoing routine contrast-enhanced MRI using Dotarem are included.

At the time of data analysis (1st April 2012), a total of 24,961 patients were included. Among them, there were 1057 pediatric patients aged 0 to 17 (mean age is 10.1 ± 5.3 years).

Out of the total patients population, renal impairment at the time of inclusion (i.e. eGFR or eCrCl < 60 ml/min (1.73m²) was described in 528 patients (2.1%). Among them, 331 patients (62.7%) were followed-up over a period of at least 3 months and had no suspicion of NSF.

Follow-up data were not yet available for the other 197 patients (37.3%) with renal impairment at the time of data analysis.

A total of 28 patients (0.11%) had at least one AE (mainly urticaria, nausea, vomiting). Most of AEs were considered as mild or moderate in intensity, and related to administration of the contrast agent. All patients recovered.

Among the pediatric population, CNS examinations accounted for 54.4% of contrast-enhanced procedures.

Among the pediatric population aged 0-17 years, 3 children had renal insufficiency (0.3%) at inclusion. No AE was reported in the pediatric population aged 0-17 years.

9.4 Post-Marketing Pharmacovigilance Experience

9.4.1 Overall Population

The post-marketing safety analysis is based on approximately 30 million doses given (cut-off date: 31 March 2012). A total of 1791 cases with 3947 reactions were reported. Adverse reaction reports received from spontaneous sources (outside the US) since the first launch in 1989 until March 2012 are consistent with the AEs observed in clinical studies and the known safety profile of Dotarem. The overall incidence of AEs is very low; it is estimated to be about 6 cases for 100,000 patients exposed, and 13 adverse drug reactions (ADRs) per 100,000 patients.

In terms of seriousness, 622 serious cases were reported. The incidence of serious cases is estimated to be about 2 serious cases per 100,000 patients exposed.

The most frequently affected body systems were:

- Skin and subcutaneous tissue disorders (26.9%), with 1061 ADRs in 770 patients
- Gastrointestinal disorders (18.4%), with 726 ADRs in 563 patients
- Respiratory thoracic and mediastinal disorders (13.7%), with 541 ADRs in 370 patients
- Nervous system disorders (7.0%), with 278 ADRs in 235 patients
- Immune disorders (6.2%), with 246 ADRs in 166 patients

In addition to the preceding reactions, a total of 24 fatal cases have been reported since the first product marketing. The cumulative incidence of fatality corresponds to 0.08 cases per 100,000 patients. In 12 fatal cases (50%), death was most likely related to anaphylaxis. Notably, however, anaphylactic shock was clearly indicated as a reaction in only 4 of these cases. In 9 of these 12 cases, cardio-respiratory reactions were the main cause leading to death. The most common cause of fatality is, therefore, cardio-respiratory related, predominantly cardiac arrhythmias, within the context of anaphylaxis.

NSF was identified as the second most common cause of fatality (8 cases). However, these cases were reported as related to multiple-agent administration with other GBCAs (5 cases) or unspecified single-agent (3 cases).

No single-agent cases of NSF or NSF-like symptoms have been received and/or reported for Dotarem, in which available clinical and histological data are consistent with a NSF diagnosis, according to the criteria of Girardi *et al* (Girardi *et al*., 2011). Non-clinical studies suggest that due to its macrocyclic structure, Dotarem exhibits the highest kinetic stability among all GBCAs and is thus expected to have a very low propensity to release free Gd^{3+}.

Post-marketing pharmacovigilance experience also confirms the absence of nephrotoxicity for Dotarem based on the very low number of renal adverse drug reactions (0.04 per 100,000 patients).

There were 3 cases of overdose (cumulatively) without associated AEs, all of which occurred in the pediatric population aged 0 to 17 years. Overall, the reactions observed in patients ≤2 years old were most frequently due to medication errors such as overdose or extravasation. The majority of cases in the 2 to 16 year-old population were associated with hypersensitivity reactions.

Based on data gathered since its launch in 1989, the risk/benefit ratio of Dotarem remains unchanged and favorable. The Guerbet Pharmacovigilance Department will continue to monitor reports of adverse experiences, including those occurring in the context of misuse, medication errors and off-label use. Reports will be collected worldwide and Guerbet will revise the safety information should evaluation of surveillance data yield significant new information.

10 NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Summary:

- Non-clinical studies performed in sensitized rat models of NSF showed that Dotarem has a high stability and did not induce any fibrotic skin lesions. The results of these studies highlight the importance of the thermodynamic and kinetic properties of the Gd complex.
- This is consistent with the macrocyclic structure of this agent and with the post-marketing experience, as no single-agent/unconfounded cases of NSF have been reported in humans treated with Dotarem although approximately 30 million doses have been administered.

10.1 Non-clinical Studies Related to the Risk of NSF

In addition to on-going clinical investigations, extensive non-clinical studies were conducted by Guerbet in collaboration with academic institutions with the aim of contributing to a better understanding of the NSF disease mechanism.

The objectives of these studies were to explore the mechanism of action of Gd-chelates to induce NSF. Since dermal fibrosis was observed in patients with severe renal insufficiency, these non-clinical studies were based on *in vitro* fibroblast and keratinocyte cell cultures and *in vivo* renal insufficiency rat models.

Indeed, NSF occurs in patients with severe or end-stage renal failure. It is speculated that longer residual time plays a critical role in the pathogenesis of the disease (Abu-Alfa *et al.*, 2011). Therefore, the effects of Dotarem have been investigated on several models of renal failure. It has been reported that hyperphosphatemia is associated with NSF in CKD patients (Marckmann *et al.*, 2007). This abnormality was found to sensitize renally-impaired rats to the profibrotic effects of a nonionic linear GBCA.

Dotarem was compared to the linear and non-ionic gadolinium chelate Omniscan, which carries a higher risk of NSF. Some studies were performed using non-formulated Omniscan, i.e., a solution with no excess caldiamide ligand. The studies conducted are summarized in Table 21.

Table 21: Non-Clinical Studies Related to the Risk of NSF – Study Designs and Main Results

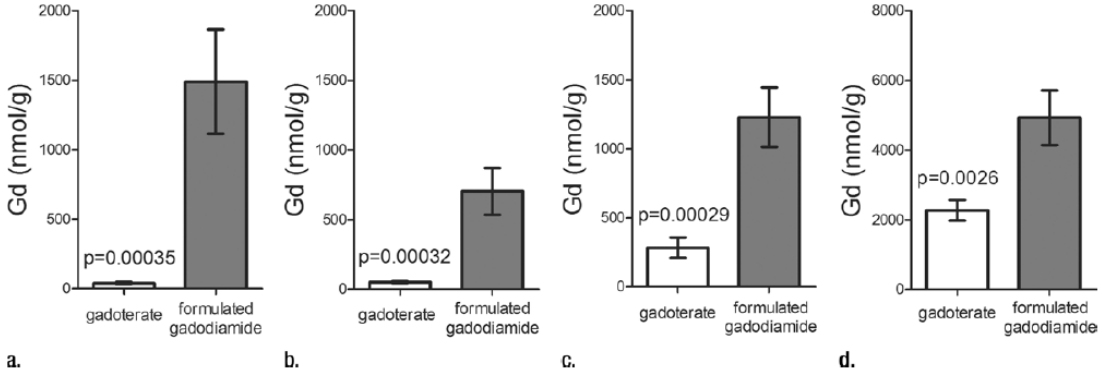
Study	Experimental Model / Methods	Salient Results
MacNeil *et al*. 2011	- Human fibroblasts and keratinocytes in culture. - Products tested: Dotarem, Gd-EDTA, Omniscan. - Incubation for 3 and 7 days up to 10 mM.	- Dotarem: little, if any, effects on fibroblasts and keratinocyte viability. - Gd complexes with lesser stability (Gd-EDTA and Omniscan) increased fibroblasts and keratinocytes viability. The increase in collagen production by human fibroblast cultured with Omniscan was secondary to stimulation of viability.
Fretellier *et al*., 2011a	- Renally impaired rats (subtotal nephrectomy). - Products tested: Dotarem, Omniscan (formulated & non-formulated). - Dose: 2.5 mmol/kg/d x 5 days, IV. - Histology (various organs, special focus on skin).	- Dotarem: very few histologic lesions, similar to the control group. - Formulated Omniscan: signs of degradation of collagen fibers in the dermis. - Non-formulated Omniscan: high morbidity and mortality. Numerous superficial epidermal lesions, inflammation, necrosis and increased cellularity in the dermis. Degradation of dermal extracellular matrix.
Fretellier *et al*., 2011b	- Renally impaired rats (subtotal nephrectomy). - Products tested: Dotarem, Omniscan (formulated & non-formulated). - Dose: 2.5 mmol/kg/d x 5 days, IV. - Histology (various organs, special focus on skin). - Measurement of total Gd concentrations by ICP-MS in skin, plasma & bone. - Measurement of dissociated free Gd in plasma by HPLC coupled to ICP-MS. - Relaxometry measurements in skin & bone to distinguish free from complexed Gd.	- No gradual dissociation of Dotarem in the skin and bone, unlike Omniscan. - No dissociated Gd in plasma of Dotarem-treated rats, unlike Omniscan 11 days after the 1st injection.

Abbreviations: Gd = gadolinium; GBCA = gadolinium-based contrast agent; HPLC = high performance liquid chromatography; ICP-MS = Inductively coupled plasma mass spectrometry; IV = intravenous; NSF = Nephrogenic Systemic Fibrosis

Study	Experimental Model / Methods	Salient Results
Haylor *et al.*, 2012	- Renally impaired rats (subtotal nephrectomy). - Products tested: Dotarem, Omniscan (formulated). - Dose: 2.5 mmol/kg/d x 5 days, IV. - Morphometric and immunohistochemistry assessments on skin, 28 days after 1st injection.	- Greater amount of Gd deposited in the skin (40-fold), bone (14-fold), liver (4-fold) and kidney (2-fold) in Omniscan-treated rats versus Dotarem-treated rats (Figure 10). - Dotarem: no Gd detected within collagen fibrils or fibroblasts. - Omniscan-treated rats: Gd retention in skin located to the collagen fibrils in both the extracellular matrix and activated fibroblasts. - No increase in dermal cell count or dermal thickness and no activated fibroblasts in dermis with Dotarem, while such effects were seen with Omniscan (Figure 11and Figure 12).
Fretellier *et al.*, 2012	- Renally impaired rats (subtotal nephrectomy) with high phosphate diet (hyperphosphatemia has been reported in patients with NSF). - Products tested: Dotarem, Omniscan (formulated), Gadavist, Multihance. - Dose: 2.5 mmol/kg/d x 5 days, IV - Histology (various organs, special focus on skin). - Measurement of total Gd concentrations by ICP-MS in skin, plasma & bone. - Measurement of dissociated free Gd in plasma by HPLC coupled to ICP-MS. - Relaxometry measurements in skin and bone to distinguish free from complexed Gd.	- Hyperphosphatemia sensitizes renally impaired rats to the profibrotic effects of Omniscan. No effect of Dotarem. - In renally impaired and hyperphosphatemic rats, no signs of toxicity of Dotarem. - 25 days after beginning of GBCA injection, a dramatic decrease in skin Gd levels was observed for all GBCA, except Omniscan (concomitant with skin lesions induced by this compound). - No gradual *in vivo* dissociation of Dotarem was observed, while such dissociation was seen with Omniscan.

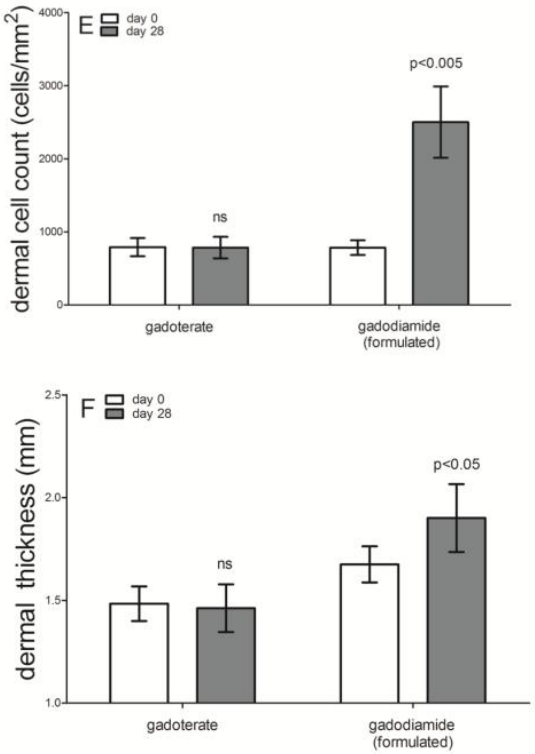
Abbreviations: Gd = gadolinium; GBCA = gadolinium-based contrast agent; HPLC = high performance liquid chromatography; ICP-MS = Inductively coupled plasma mass spectrometry; IV = intravenous; NSF = Nephrogenic Systemic Fibrosis

Figure 10: Total Gadolinium Concentration in the (a) Skin, (b) Bone, (c) Liver and (d) Kidney of Renally Impaired Rats Following Treatment with Dotarem or Omniscan



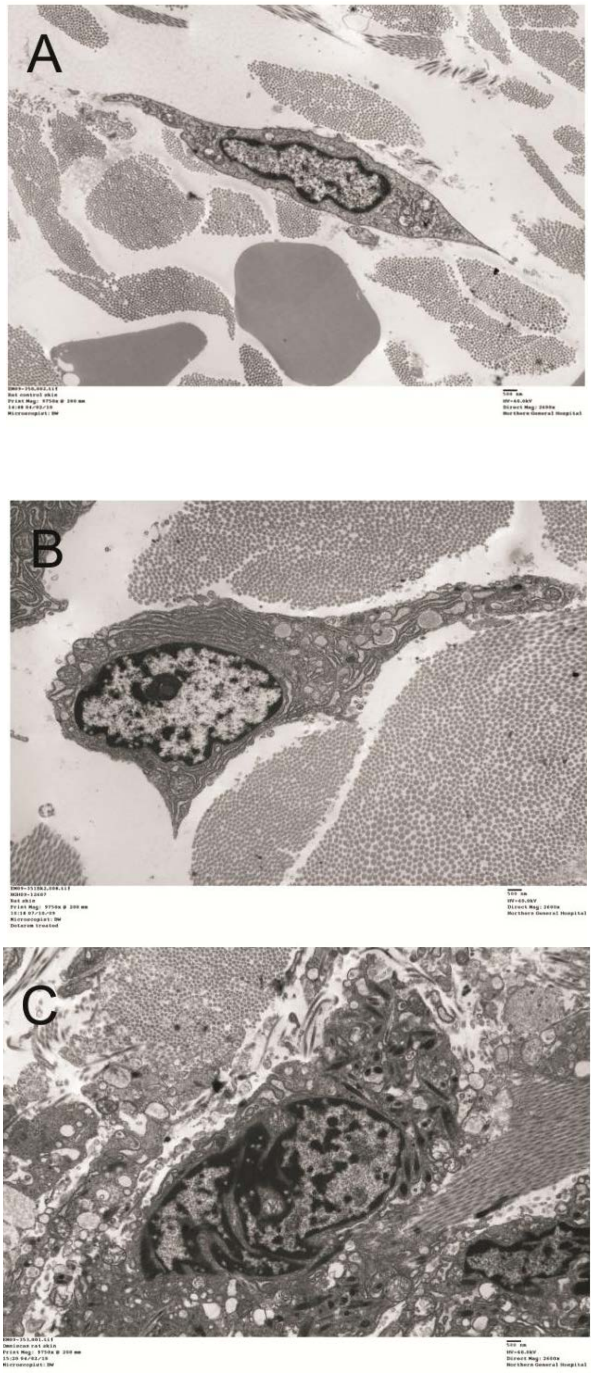
Abbreviations: Gd = gadolinium
Gadoterate = Dotarem®; Gadodiamide = Omniscan®
Source: Haylor *et al.*, 2012

Figure 11: Dermal Cell Count and Dermal Thickness Measured Before (Day 0) and 28 Days after Administration of Dotarem or Omniscan in Renally Impaired Rats



Gadoterate = Dotarem; Gadodiamide = Omniscan
Source: Haylor *et al.*, 2012

Figure 12: Electron Microscopy in the Dermis



Typical fibroblast observed at electron microscopy in the dermis of (A) saline-treated rat, (B) Gadoterate meglumine-treated rat (inactive fibroblast, rough endoplasmic reticulum) and (C) Omniscan (activated fibroblast containing electron-dense collagen fibrils fragments together with occasional electron-dense spots within collagen bundles) (X 2600).

Source: Haylor *et al.*, 2012

The studies conducted and summarized above showed that Dotarem has a high stability and did not induce any fibrotic skin lesions in sensitized rat models of NSF. The results of these studies highlight the importance of the thermodynamic and kinetic properties of the Gd complex. A low propensity of NSF events can be anticipated with Dotarem use, based on these studies performed in sensitized non-clinical models. This is consistent with the macrocyclic structure of this agent and with the post-marketing experience, as no single-agent cases of NSF have been reported in humans treated with Dotarem.

10.2 NSF Data from Clinical Studies and Post-Marketing Observational Studies

10.2.1 Clinical Studies

During the clinical development program of Dotarem, no cases of NSF and/or NSF-like symptoms were reported in the 2813 patients receiving Dotarem (at dose up to 0.3 mmol/kg BW).

10.2.2 Prospective Post-Marketing Observational Study including NSF Surveillance

A worldwide prospective post-marketing observational study short named SECURE is ongoing and targets to obtain an international database of 40,000 patient examinations (adults and children) and to examine the general safety profile of Dotarem. In addition, for patients with renal insufficiency, a follow-up of at least 3-months is performed in order to collect any sign of suspected NSF.

At the time of data analysis (April 1, 2012), a total of 24,961 patients were included.

Out of the total patients population, renal impairment at the time of inclusion (i.e. eGFR or eCrCl < 60 ml/min (1.73m²) was described in 528 (2.1%) patients. Among them, 331 (62.7%) were followed-up over a period of at least 3 months and had no suspicion of NSF. Follow-up data were not yet available for the other 197 (37.3%) patients with renal impairment at the time of data analysis.

10.3 Post-Marketing Experience

Until 2006, few side effects had been reported with GBCAs for MRI. These agents have been shown to be well tolerated by the vast majority of over 200 million patients exposed to gadolinium since the late 1980s: side effects associated with Gd-chelates are usually mild to moderate in severity (Runge *et al.*, 2001). As a consequence, they are considered to be among the safest agents used in humans (Li *et al*., 2006).

However, with the rapidly expanding body of literature linking some GBCAs to NSF, awareness of the potential side effects and adverse reactions with Gd-chelates has become an important consideration for practicing radiologists and specialists. NSF, although rare, is to be considered as a serious late adverse reaction in patients with severe to terminal renal insufficiency (ACR Manual on Contrast Media, 2010).

In July 2010, based on the analysis of all available data regarding NSF (with sources including health authorities, industry and academic centers), the European Medicines Agency (EMA) published an opinion leading to revision of the labeling of all the GBCAs. This opinion confirmed a previous EMA classification of these agents with regard to the risk of NSF (high, medium or low risk).

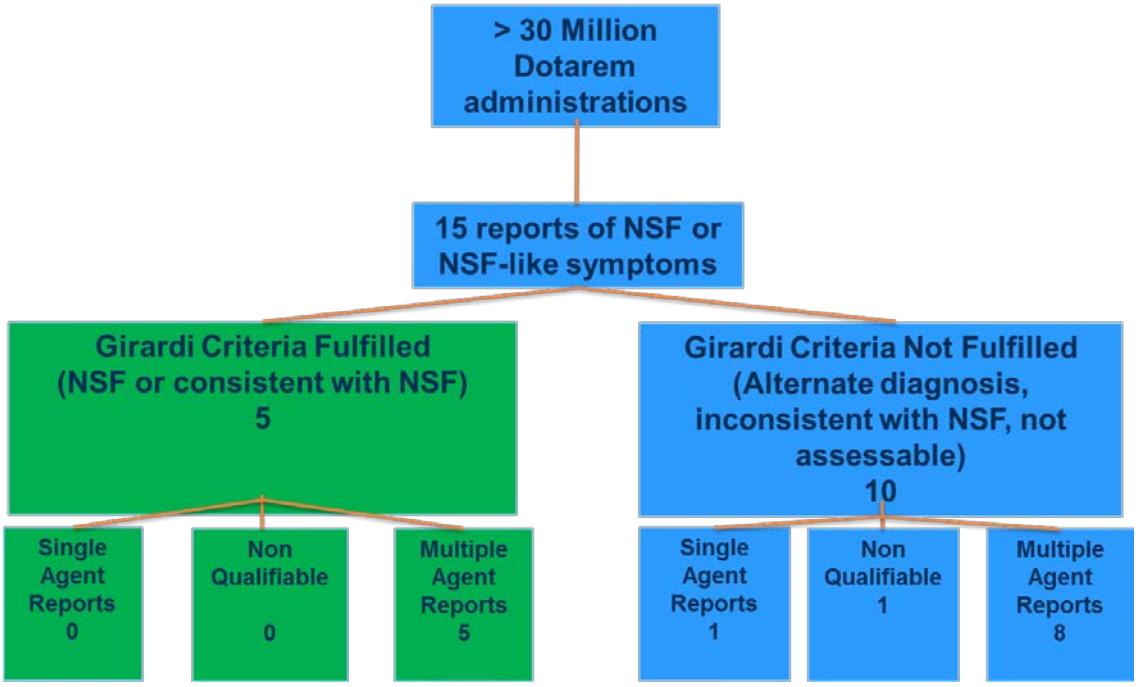
In a similar analysis, the US FDA published its decision regarding the US prescribing information of GBCAs in September 2010. Because of this decision, products considered as high risk in the EU are now contraindicated in patients with severe chronic or acute renal insufficiency. For all products, it is now mandatory in the US to screen (by interview and clinical examination) all patients for renal insufficiency, and a lab test for renal function is mandatory for patients identified as at risk.

Radiologists and radiographers should evaluate the medical history of the patient before the administration of Gd-chelates and identify patients with severe renal impairment (i.e., GFR or eGFR <30 mL/min/1.73 m²), and check whether the intended product is authorized in this specific population.

The recently revised EU labeling of Dotarem now includes a new statement in the section on Posology and Method of Administration, requiring that only the minimum diagnostic dose is injected in patients with severe renal impairment (GFR <30 mL/min/1.73 m^2) and in patients in the perioperative liver transplantation period, a dose not exceeding 0.1 mmol/kg body weight, with no repeated dose in one MRI and at least 7 days between injected MRIs. The section on Special Warnings and Precautions for Use has been revised accordingly, with a recommendation for a screening with lab tests in patients with impaired renal function, and recommendations on hemodialysis.

As reported in the Dotarem Post Marketing Experience Safety Report, cumulative review from 08 March 1989 to 31 March 2012, a standardized Guerbet MedDRA Query was specifically established by Guerbet to search for potential cases of NSF. Based on that search for NSF signal, 346 events were retrieved, pertaining to 313 cases. Most of the events retrieved were non-specific and 38 cases of NSF were identified (in which the MedDRA term "Nephrogenic Systemic Fibrosis" was coded as adverse reaction). Among the 38 reported cases, Dotarem was administered in only 15 medically confirmed cases. A summary of these 15 cases is presented in Figure 13.

Figure 13: Post-Marketing Reports of NSF or NSF-Like Symptoms with Dotarem



Overall, the cumulative review of the suspected NSF cases confirms the absence of single-agent/unconfounded cases in which the clinical and histological diagnosis of NSF is consistent with the Girardi criteria (Girardi *et al*, 2011). The benefit/risk ratio of Dotarem remains favorable and the likelihood of it causing NSF remains very low.

10.3.1 Additional Analyses of NSF Reports

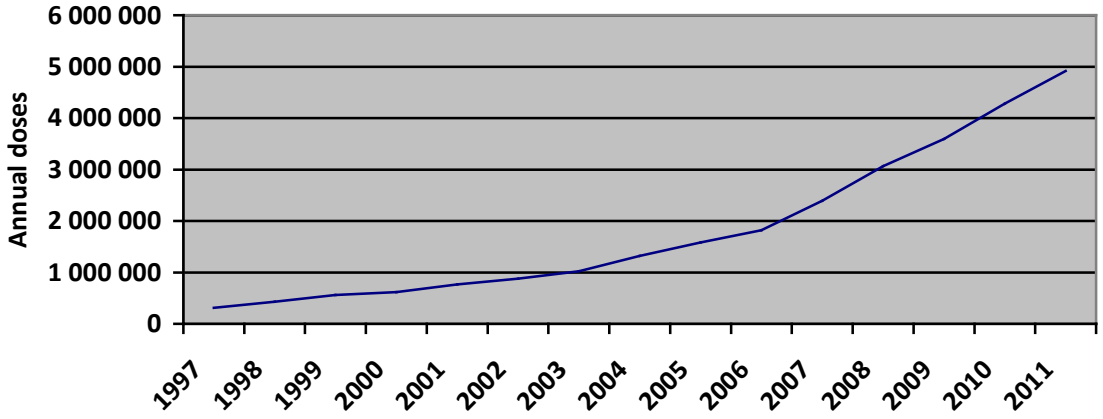
10.3.1.1 NSF Reports by Year

Between the launch of Dotarem and the cut-off date for this analysis (March 31, 2012), approximately 30 million patients are estimated to have been exposed to Dotarem.

From 1997 to end of 2011, the estimated number of administrations of Dotarem has increased approximately 15-fold to approximately 4.9 million administrations for 2011. The increase in usage of Dotarem was especially pronounced since 2006 when first regulatory actions were taken in the context of GBCAs and the potential to trigger NSF.

Figure 14 shows the increasing number of world-wide Dotarem administrations, while Table 22 shows that the number of NSF or NSF-like reports each year have remained low.

Figure 14: Annual Doses of Dotarem Worldwide



All reports were received by Guerbet from 2007 onwards, however, the onset (when known) occurred between 1999 and 2010 (Table 22). The last documented administration of Dotarem in any of these 15 reports was May 2010 (single agent/NSF diagnosis not confirmed).

Table 22: Reports of NSF by Year

Year of Onset of Signs and Symptoms	Number of Multiple-agent Reports	Number of Single-agent Reports
1999	1	
2000	1	
2001	1	
2002	2	
2003	1	
2004	4	
2005	1	
2006	2	
2010		1*
Unspecified or unclear	1	
Total	14	1*

* case not fulfilling the Girardi 2011 criteria

10.3.1.2 NSF Reports by Age and Gender

Among the 15 reports, there were 9 male and 5 female patients (for one patient, the gender was not known). When known, the age ranged from 34 to 82 years, and was unknown for 2 patients (Table 23).

Table 23: NSF Reports by Age and Gender

		Number of Reports
Age (years)	30 – 39	3
	40 – 49	3
	50 – 59	1
	60 – 69	4
	70 – 79	1
	80 +	1
	Unknown	2
Gender	Male	9
	Female	5
	Unknown	1

10.3.1.3 NSF Reports by Patient Renal and Dialysis Status

Almost all patients presented with renal impairment (unknown for 2 cases), from "reduced kidney function" to end-stage renal disease and kidney transplantation.

The renal status of these patients is presented in the table below. Patients can present more than one renal condition (Table 24).

Table 24: Renal Status

Renal condition	Number of Patients
Renal failure (incl. severe failure)	7
Reduced renal function	2
End stage renal disease	1
Stage III renal failure	2
IgA or diabetic nephropathy	2
Nephrectomy	1
Renal transplantation	2
Decreased creatinine clearance	1
Increased serum creatinine	1
Total	19

Dialysis status is presented below; 9 patients were undergoing dialysis (Table 25).

Table 25: Dialysis Status

	Number of Patients
Dialysis	2
Transperitoneal dialysis	2
Hemodialysis	5

10.3.1.4 NSF Reports by Gadolinium Administration

The patients described in the 15 reports received between 1 and 7 GBCA administrations before onset of NSF signs/symptoms, with 14 of these patients known to have received more than one GBCA administration (Table 26).

Table 26: GBCAs Administrations before NSF Onset

Number of GBCA Administrations Before Onset of NSF Signs/Symptoms	Number of Patients
1	1
2	7*
3	2
4	1
5	2
7	2
Total	15

Abbreviations: NSF = Nephrogenic Systemic Fibrosis
* Two patients actually received Dotarem after the onset of the first NSF signs/symptoms (one patient with 2 other GBCA and one patient with 2 administrations of the same GBCA).

The dose of Dotarem is known for 11 cases and unknown for 2 cases. In addition, for other 2 reports, limited information is available on the dose (cumulative dose combined with another GBCA). Where the dose of Dotarem was provided, patients received individual volumes ranging from 14 to 40 mL.

In the 5 multiple-agent reports fulfilling the Girardi criteria, patients received between 2 and 7 administrations of GBCA before the onset of symptoms. Four patients had administrations of both Dotarem and Omniscan.

10.3.1.5 NSF Reports by Identity of GBCA Administered

GBCAs identified in the 15 reports are provided in Table 27.

Table 27: GBCAs Identified in the NSF Reports

	Dotarem	Gadovist	Magnevist	Omniscan	Prohance	Unspecified	Number of Patient
Single agent	X						1**
Multiple agents	X			X			7
	X		X	X			2
	X			X*	X*		1
	X	X	X				1
	X					X	1
				X		X	1+
			X	X			1+
Total							15

* case where exact GBCA has not been identified (Omniscan or Prohance has been administered to the patient in addition to Dotarem).
** case not fulfilling the Girardi 2011 criteria
+ 2 patients received Dotarem after onset of first signs of NSF

10.3.1.6 NSF Reports by Country

The country of origin for the 15 reports is provided in Table 28. No particular conclusion can be drawn from this data, although 40% have been received from Switzerland.

Table 28: NSF Reports by Country

Country	Number of Reports
Austria	3
Belgium	1
Denmark	3
France	1
Japan	1
Switzerland	6
Total	**15**

10.4 Literature Report

There are case reports in the literature describing 4 observations with reports of NSF or NSF-like symptoms (Elmhodt *et al.*, 2011; Hatta *et al*., 2012; Heinz-Peer *et al*., 2010; Lemy *et al*., 2010). These reports are included in the summary of reports described above.

11 EFFICACY AND SAFETY IN PEDIATRIC PATIENTS UNDER 2 YEARS OF AGE

During the Dotarem pre-NDA meeting held on 12th June 2012, it was agreed between the FDA and Guerbet to include the available data from clinical and post-marketing studies to support the proposed CNS indication for the pediatric population less than 2 years of age.

Summary:

The 3 clinical studies and the 6 prospective post-marketing observational studies that included a total of 241 pediatric patients less than 2 years of age provided a good level of efficacy and safety, consistent with those found for adult patients and pediatric patients older than 2 years of age.

Overall, in terms of safety:

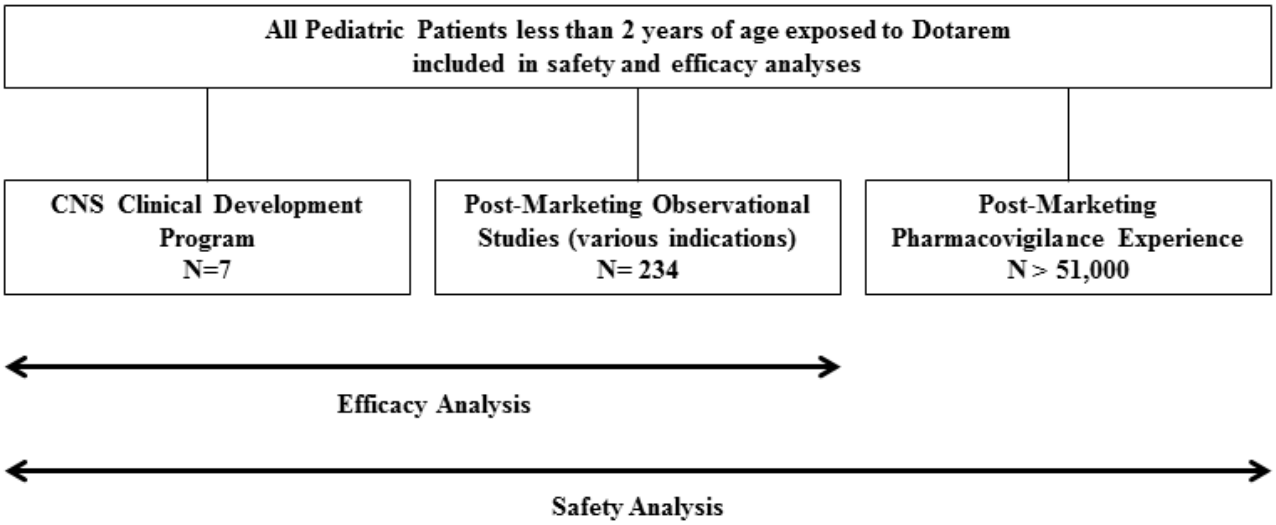
- In clinical studies, there were no related AEs as reported by investigators. However, one AE was temporarily associated to the administration of Dotarem (mild vomiting occurred in one female patient who did not required treatment).
- In post marketing observational studies, no AE were reported by investigators.
- In post marketing setting, 8 pediatric patients have reported 10 ADRs, including one serious ADR. The reactions observed in pediatric patients less than 2 years of age were mostly due to medication errors (such as overdose) or extravasation. No anaphylactic reactions, SAE, or deaths have been reported
- No NSF events were described in this population in clinical studies, post-marketing observational studies and post marketing experience.

Overall, based on clinical studies (N=7 patients), post marketing observational studies (N=234 patients) and post marketing experience (N>51000 patients), the safety and efficacy data of Dotarem provide a good level of confidence regarding the benefit risk ratio for the pediatric population less than 2 years of age.

11.1 Data Presented in this Section

For the population of pediatric patients less than 2 years of age, the efficacy and safety data available are summarized in Table 15.

Figure 15: Patients Breakdown for Efficacy and Safety Analysis of Dotarem in Patients Less than 2 Years of Age



11.2 Efficacy Data

11.2.1 Efficacy Data from Clinical Studies

During Dotarem development in Europe between 1988 and 1991, 3 non-randomized studies (DGD-3-15, DGD-3-16 and DGD-3-29) were conducted by Guerbet and collectively enrolled 99 pediatric patients from 1.2 months to 17 years, including 7 pediatric patients less than 2 years of age, leading to marketing authorization of Dotarem in CNS indication in this class of age (Appendix 1).

The distribution was as follows:

- DGD-3-15: 29 pediatric patients, including 3 less than 2 years of age
- DGD-3-16: 20 pediatric patients, including 2 less than 2 years of age
- DGD-3-29: 50 pediatric patients, including 2 less than 2 years of age

For all the pediatric patients, the recommended dose in the protocol was consistent with the currently proposed pediatric dose in the US: 0.1 mmol/kg (i.e., 0.2 ml/kg).

Table 29 summarizes the actual dose injected in these patients.

Table 29: Dose (mmol/kg) Actually Administered

Unit	mmol/kg
N	7
Mean	0.1
Median	0.1
Min/Max	0.10/0.11

Abbreviations: Max = maximum ; Min = minimum

These 3 studies used a slow injection rate:

- DGD-3-15: Flow rate ranged from 2 to 5 mL/min (3 mL/min for the 3 patients under 2 years of age)
- DGD-3-16: Flow rate ranged from 1 to 3 mL/min
- DGD-3-29: Flow rate was slow IV injection (actual rate not collected).

The anatomic CNS imaging is a steady state imaging, which means the acquisition of images is done at least 5 to 10 minutes after injection, after uptake of the contrast agent by the lesion (resulting from BBB disruption). Consequently, the efficacy of Dotarem in cerebral anatomic imaging does not depend on the injection rate of the product and efficacy can be considered similar when the product is injected slowly (infusion) or rapidly (bolus).

These 3 studies used magnetic resonance for imaging of various neurological lesions. Overall, the observed results were similar to those already described with adult patients and pediatric patients above 2 years of age. Dotarem enhanced-MRI allowed better visualization of lesions with a more accurate delineation of the lesion/normal tissue or lesion/edema borders. For the global population included in these 3 studies, this better visualization modified the planned therapeutic approach in 15% to 34% of cases.

More specifically for the 7 pediatric patients less than 2 years of age, the efficacy results are described in Table 30.

Table 30: Efficacy Results for Pediatric Patients Less Than 2 Years of Age

Patient ID Number (Age)	Study	Indication	Results for Efficacy Endpoints
16 (0.1 yr)	DGD-3-15	Etiologic diagnosis of an abscess lesion	Enhanced MRI confirmed the absence of lesion assessed by unenhanced MRI
19 (0.5 yr)	DGD-3-15	Etiologic diagnosis of a meningioma	Good contrast uptake allowed better assessment of lesion delineation and vascularization. Better diagnostic contribution after Dotarem when compared to unenhanced MRI resulting in a treatment change
21 (1.5 yr)	DGD-3-15	Etiologic diagnosis of a pathological abscess	Enhanced MRI confirmed the absence of lesion assessed by unenhanced MRI
1 (0.5 yr)	DGD-3-16	Staging of a corpus callosum tumor	Complementary diagnostic contribution of MRI after Dotarem because the absence of enhancement after contrast injection provided information on the type of tumor
18 (1.8yr)	DGD-3-16	Staging of a rhabdomyosarcoma	Unenhanced MRI not performed because child was too tired. Diagnostic contribution of Dotarem enhanced MRI due to contrast uptake by the lesion
2 (1 yr)	DGD-3-29	Post-surgical control of a residual tumor (ependymoma) of the 4th ventricule	After Dotarem, better lesion delineation from parenchyma and arterial trunks. Size and location of the tumor better evaluated
14 (1.5 yr)	DGD-3-29	Treatment follow-up of a residual ependymoma of the posterior fossa with supratentorial localization	Diagnostic more specific after Dotarem and therapeutic decision facilitated.

In conclusion for these 7 patients included in 3 different clinical studies, Dotarem-enhanced MRI provided a good diagnostic contribution and allowed a better patient management.

11.2.2 Efficacy Data from Prospective Post Marketing Observational Studies

In addition, 6 prospective post-marketing observational Guerbet-sponsored studies included a total of 234 pediatric patients less than 2 years of age (Neiss, 1991; Briand, 1992; Maurer, 2012; Ishiguchi, 2010; Emond, 2011; SECURE ongoing study - 01 April 2012 interim analysis).

The distribution for this age group was as follows:

- Neiss 1991: 6 pediatric patients
- Briand 1992: 26 pediatric patients
- Ishiguchi 2010: 2 pediatric patients
- Emond 2011: 104 pediatric patients
- Maurer 2012: 10 pediatric patients
- SECURE ongoing study: 86 pediatric patients in 01 April 2012 interim analysis.

In these 6 studies, according to local package inserts of participating countries, the recommended dose was 0.2 ml/kg (i.e., 0.1 mmol/ kg).

The administration in pediatric patients was performed as a bolus injection (around 1-2 mL/sec) and was similar to the clinical practice established at the time of the study.

As previously mentioned, injection rate does not affect the efficacy of Dotarem as CNS lesion evaluation is done in steady state imaging (after Dotarem captured by the lesion).

In general, due to body weight of pediatric patients less than 2 years of age, the injection volume is very small, and consequently, clinical practice cannot rely on calculated rate of injection. However, the injection should be manually controlled when administering bolus to avoid any damage to the delicate veins of pediatric patients.

The study population of less than 2 years of age included in these studies is described in Table 31.

Table 31: Study and Population Characteristics in Post Marketing Observational Studies for Pediatric Patients Less than 2 Years of Age

Study / Reference (Number of Patients)	Study design	Gender (Female/Male)	Age or Mean Age (Year or Month)	Indication of Examination
European PMS Neiss, 1991 (N=6)	Not-randomized, open label, multicenter	5 Females, 1 Male	1 to 1.5 year	CNS
French PMS Briand, 1992 (N=26)	Not-randomized, open label, multicenter	not available	not available	CNS in most cases
Japanese PMS Ishiguchi, 2010 (N=2)	Not-randomized, open label, multicenter	2 Females	1 month 20 months	CNS (1) Chest (1)
French PMS Emond, 2011 (N=104)	Not-randomized, open label, single-center	58 Males, 45 Females, 1 unknown	8.1 ± 5.2 months (range: 3 days to 18 months)	CNS in most cases (see details in the following table)
German PMS Maurer, 2012 (N=10)	Not-randomized, open label, multicenter	2 Males, 7 Females, 1 unknown	8.7 ± 3.2 months	Neurological : 6 Musculoskeletal: 3 Unknown: 1
International PMS SECURE ongoing study – cut-off date of 1st April 2012 (N=86)	Not-randomized, open label, multicenter	44 Males, 42 Females	0.8 ± 0.4 year (range: 0-1.9)	CNS: 70 (81.4%) Whole Body : 6 (7%) Musculoskeletal : 7 (8.1%) Angiography : 1 (1.2%) Others: 2 (2.3%)

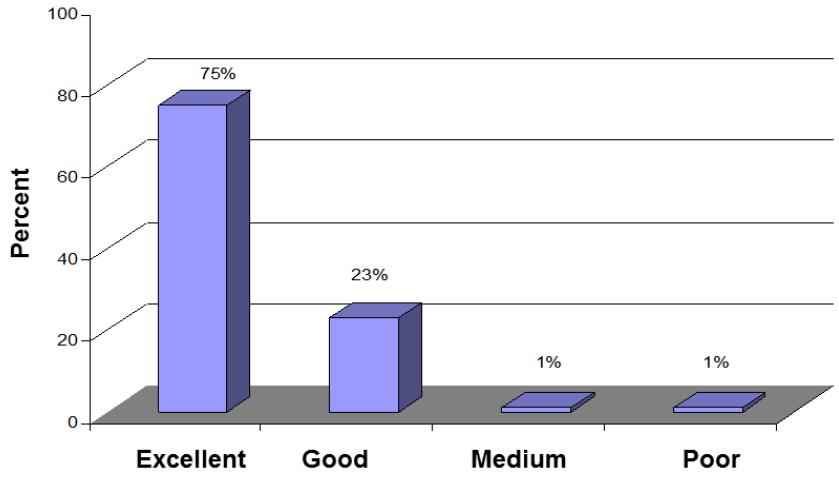
Abbreviations: CNS: central nervous system ; PMS= Post Marketing observational Study

Because of the variability of efficacy endpoints in these studies, the efficacy results cannot be pooled for the whole population included in these 6 studies. For some of them, the number of pediatric patients less than 2 years of age is low. However, in the largest study Emond 2011 including only patients up to 18 months of age, the indications for MRI examination and the corresponding results are described in Table 32 and Figure 16.

Table 32: Indications for Dotarem MRI in Emond 2011 Study

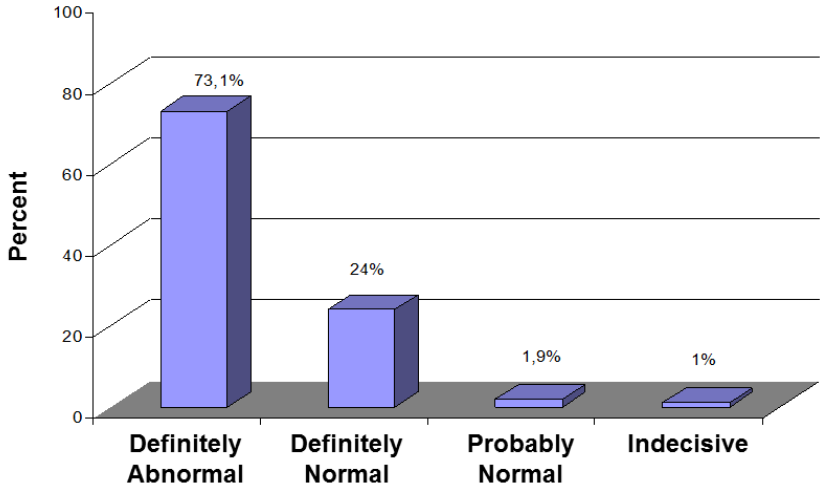
Indication Group (several indications possible per patient)	Pediatric Patients (Percent of Total)	Listing of Findings in Abnormal Scans
Primary diagnosis	64 (50.8%)	-Infection with meningeal enhancement -Vascular and/or lymphatic malformations (hemangiomas, hemolymphangiomas, cystic lymphangiomas -Coccygeal fistulae, dysraphia -Sturge-Weber malformation in facial angioma -Presence of tumoral lesions
Evaluation of the extension of a known condition	40 (31.7%)	-Metastasis, multiple localization -Hemangioma (intra-orbital extension or bone extension) -Vascular and/or lymphatic malformation (vascular or cystic anomaly) -Infection (abscess) -Dermal fistula associated with dermal angioma (intradural extension)
Post-operative control	14 (11.1%)	-Tumor (recurrent, residual) -Dermal fistulae
Follow up	8 (6.3%)	-Infection -Tumor -Dysraphism

Figure 16: Image Quality in Emond 2011 Study (N= 104)



The Image Quality was rated as good or excellent in 98% of the patients.

Figure 17: Diagnostic Contribution in Emond 2011 Study (N= 104)



After Dotarem injection, Diagnostic was clearly made for 97% of the patients.

Whatever the indication for Dotarem enhanced MRI (primary diagnosis, staging, post-operative control or follow-up), a better patient management could be achieved.

In conclusion, the results obtained from 6 prospective post-marketing observational studies showed the efficacy of Dotarem in various neurological pathologic conditions in pediatric patients less than 2 years of age. These data confirmed the efficacy of Dotarem is consistent in all patient populations studied, adult and pediatric patients from 3 days to 17 years.

11.3 Safety Data

11.3.1 Safety Data from Clinical Studies

Three supportive pediatric studies included 7 pediatric patients less than 2 years of age. The safety endpoints assessed for these patients are described in Table 33.

Table 33: Safety Parameters Assessed in Clinical Studies in Pediatric Patients Less than 2 Years of Age

Study Name	Patient Number	Clinical Laboratory Evaluations	Clinical Follow up Duration
DGD-3-15	3	Standard biochemistry and hematology	2 hours and 24 hours
DGD-3-16	2	No	20 minutes
DGD-3-29	2	No	45 minutes
Total Number	7	-	-

No history of allergy was described for any of these patients. Five of them had concomitantmedications (pentothal for 1 patient, fluothane + pentothal for 2 patients, sodium oxybate for 2 patients).

According to the protocol, they all received Dotarem at a dose of 0.1 ± 0.01 mmol/kg at slowflow rate (between 1 and 3 mL/min).

Only one AE occurred in one female patient (patient 18 in DGD-3-16 study). She experienced vomiting 20 minutes after Dotarem infusion. The AE was of minor intensity, short duration and required no treatment. The child was receiving sodium oxybate asconcomitant medication. There was a temporal relationship between the AE and both medications. However, the investigator assessed the AE not related to Dotarem.

11.3.2 Safety Data from Post Marketing Observational Studies

Six prospective post-marketing observational studies included a total of 234 pediatric patients less than 2 years of age.

The recommended IV dose was 0.1 mmol/kg according to the approved package insert in the participating countries.

According to local clinical practices, the patient follow up duration varied in the different studies and was up to 2 hours after Dotarem administration.

No AEs have been reported for these 234 patients.

11.3.3 Safety Data from Post Marketing Experience

Based on the percentage of Dotarem exposure (0.27%) for pediatric patients less than 2 years of age in France in 2011, the estimated Dotarem exposure for pediatric populations (0-2 years of age) in the countries where Dotarem is approved for use has been calculated. According to this calculation and from data collected from Europe, South Korea, Taiwan, Mexico and Brazil, the estimated number of pediatric patients less than 2 years of age injected with Dotarem between 2005 and 2012 was estimated to be over 51,000.

In the post-marketing setting, 10 ADRs have been reported for 8 pediatric patients, including one serious ADR.

These 8 pediatric patients included 7 boys and 1 girl with a mean age of 8.9 months (min: 14 days; max: 2 years). Six patients were administered Dotarem for CNS MRI and one for angiocardiac MRI; one patient was exposed via breast feeding (Table 34).

Table 34: Indication of Dotarem Administration in Patients under 2 Years

Indication		Number of Patients
CNS MRI	Arachnoid cyst Cerebral herpetic infection localization Suspicion of meningitis Brain exploration in context of neurofibromatosis Monitoring of ependymoblastoma (right ponto cerebellar corner) Unspecified	6
Angiocardiac MRI	Heart-vessel congenital malformation	1
Accidental exposure	Breast feeding	1

Abbreviations: CNS = central nervous system; MRI = magnetic resonance imaging

Note: These 8 cases occurred in France (5 cases), Sweden (2 cases) and Germany (one case).

The majority of these cases were associated with various medication errors. The most frequently reported terms were Overdose and Accidental overdose (3 cases), but no associated AEs were reported in these cases. The second most frequent term was Extravasation (2 cases). No NSF case was reported.

The 3 cases of overdose/accidental overdose were reported in patients (aged 1 month, 13 months and 16 months) who received 6-8 times the recommended dose. There were no AEs following administration and the outcome was favorable in all 3 patients. They were kept at the hospital for a short time for observation.

Two non-serious cases of extravasation involved patients aged 14 days and 2 years. The youngest patient developed an injection site induration; the extravasation involved the total volume injected (0.5 ml). The site of administration was on the back of the hand, which tends to be a fragile site in pediatric patients. The outcome was favorable after postural drainage. The other case involved an extravasation of a quarter of the dose administered at the wrist (4 ml administered in total); the outcome was favorable without complications.

The only serious event that was not associated with a medication error was an event of heart rate decrease followed by spontaneous recovery. This event involved hospitalization/hospitalization prolonged due to decreased heart rate (from 110 to 65 bpm), which was reported in an 11 month-old boy after administration of Dotarem, Largactil (chlorpromazine) and Elma patches (lidocaine, prilocaine); all 3 medications were considered suspect by the reporting Health Authority. The outcome was spontaneous recovery within minutes, after the MRI investigation was interrupted.

One case of erythema in a 1 month-old girl occurred a short time after the investigation and resolved soon after. Other concomitant medications included anesthetic agents received at the time of administration of Dotarem, which may have contributed to the onset of the event.

There was one case of exposure during breastfeeding in a 5 month-old boy (medical history of G6PD deficit). He developed tremors 5 days after his mother received Dotarem for an unknown indication. The outcome was favorable. It is important to note that breastfeeding was interrupted for 24 hours after Dotarem administration. According to the mother's physician, the relationship between tremors and Dotarem was not related.

Overall, the reactions observed in pediatric patients less than 2 years of age were most frequently due to medication errors (such as overdose) or extravasation. Although caution should be exercised in the pediatric population, no additional safety concerns have been identified in this population. Reactions most frequently reported in older age groups, such as hypersensitivity/anaphylactic reactions, have not been reported in the pediatric population less than 2 years of age.

12 BENEFIT/RISK PROFILE AND CONCLUSIONS

12.1 Benefit/Risk Considerations

This New Drug Application focuses on the efficacy and safety of Dotarem with MRI in the brain (intracranial), spine and associated tissues in adult and pediatric patients (neonates to 17 years of age) to visualize areas of disruption of the BBB and/or abnormal vascularity. The product is approved for use in more than 70 countries since 1989. Dotarem has an extensive post-marketing experience and it is estimated that approximately 30 million doses have been administered through 31 March 2012.

The 2 pivotal Phase III studies and 21 supportive CNS studies are included in the application to demonstrate the efficacy and safety of Dotarem in patients from 1.2 months to 97 years of age who benefited from Dotarem-enhanced MRI procedures for the diagnosis of various suspected cerebral or spine lesions, the detection of local recurrence of disease, the exploration of the anatomical structure of lesions or as a routine procedure for therapeutic follow-up reasons.

For pediatric patients less than 2 years of age, the results obtained from 3 clinical studies and 6 post-marketing observational studies confirmed the efficacy of Dotarem in various neurological pathologic conditions (patient age 3 days-17 years). In addition, exposure to Dotarem in over 51,000 patients less than 2 years of age is estimated based on the use of Dotarem outside US. Altogether, these data and post-marketing experience represent more data than is typically available for a New Drug Application to demonstrate efficacy and safety in a subgroup population.

Dotarem, with its unique physical characteristics of high kinetic and thermodynamic stability, complemented by a substantial body of evidence to characterize the safety and efficacy of the product gathered over more than 2 decades of use worldwide, presents a positive benefit/risk ratio. This also applies to special populations such as patients less than 2 years of age and patients with severe renal impairment. Importantly, Dotarem presents a very low risk of inducing NSF.

12.2 Benefits

12.2.1 General Population

Dotarem presents a unique chemical structure: macrocyclic and ionic gadolinium complex. This results in the highest kinetic and thermodynamic stability among all GBCAs. These parameters have been identified as critical to reducing the risk of disassociated gadolinium *in vivo* and *in vitro*. Disassociated gadolinium is suggested to be linked with the risk of triggering NSF in patients with severe renal impairment. The most stable known GBCA is Dotarem because of its macrocyclic and ionic chelate properties, while the least stable agents are the non-ionic linear chelates. Dotarem has relaxivity properties ensuring signal enhancement and MRI efficacy for diagnostic imaging and lesion visualization performance.

The efficacy of Dotarem in 2 pivotal Phase III clinical studies has demonstrated consistent improvement of Dotarem-enhanced MRI over non-enhanced MRI in term of lesion visualization in CNS. This improved lesion visualization leads either to the confirmation of the referral diagnosis or allows the exclusion of certain pathology, and thus has positively influenced patient management. Furthermore, Dotarem-enhanced MRI also showed superiority for both image quality and diagnostic confidence. Additional analyses from supportive studies demonstrated that the efficacy of Dotarem is consistent across demographic and disease subgroups.

Dotarem offers significant diagnostic advantages and improved contrast-enhanced imaging in all patients requiring CE-MRI of the CNS, including patients at risk.

12.2.2 Pediatric Population Less Than 2 Years of Age

There is an unmet medical need for MRI contrast agents in pediatric patients less than 2 years of age in the US.

MRI techniques are gaining popularity in pediatric imaging, mainly because they provide high soft-tissue contrast, allow multi-planar visualization and do not use ionizing radiation. CE-MRI offers major advantages over non-enhanced images (Auger, 2001). There is no GBCA approved in the US for use in patients less than 2 years of age. The current practice for diagnostic or disease management in this population uses currently approved GBCAs as an “off-label” application in the US. Indications of CE-MRI in neonates in the CNS includes use in infectious and inflammatory disease, congenital anomalies and neoplastic processes. CE-MRI has played a role in medical practice in the US when careful imaging is needed for the accurate assessment and the subsequent treatment plan for neonates.

The results obtained from 3 clinical studies and 6 prospective post-marketing observational studies showed the efficacy of Dotarem in various neurological pathologic conditions in pediatric patients less than 2 years of age.

Dotarem has been approved for use in the CNS in pediatric patients less than 2 years of age outside the US based on the same clinical study data as presented here. The safety of Dotarem has been well established in post-marketing use of an estimated 51,000 patients less than 2 years of age. Based on results from clinical studies, prospective post-marketing observational studies and post-marketing experience, Dotarem was well tolerated in pediatric patients, including those less than 2 years of age. Accumulated safety data in pediatric patients do not differ from what is currently known in the adult population.

12.3 Risks

The general risk for this class of gadolinium-based agents is well known and characterized across all agents approved for use in the US. Additional measures for mitigating the risk of NSF, specifically for patients with chronic and severe kidney disease, have been adopted in the US.

12.3.1 NSF

NSF is a rare, but serious, disease predominantly observed in patients with chronic and severe kidney disease (GFR <30 mL/min/1.73 m^2) or acute renal injury. A potential association with GBCAs was first reported in 2006. While the exact cause is unknown and considered multi-factorial, free gadolinium ions (Gd^{3+}) released from GBCAs are strongly suspected to play a major role in the mechanism of NSF.

Physico-chemical and non-clinical studies suggest that GBCAs with amacrocyclic and ionic structure exhibit the highest kinetic stability among all GBCAs and thus are expected to have the lowest tendency for releasing free Gd^{3+}. Based on studies performed in sensitized non-clinical models, a low propensity of NSF events can be anticipated with Dotarem use. This conclusion is also consistent and supported by post-marketing surveillance data from approximately 30 million doses of Dotarem administered to patients with no single-agent reports of NSF or NSF-like symptoms reported (Girardi *et al*., 2011).

12.3.2 Pediatric Population Less Than 2 Years of Age

There was no evidence of an increased incidence of AEs among pediatric patients. The 3 clinical studies and the 6 prospective post-marketing observational studies that included a total of 241 pediatric patients less than 2 years of age reported no related AEs. To date, NSF events have not been reported in this population. Based on these clinical studies and supported by the results of the prospective post-marketing observational studies, Dotarem has shown an acceptable overall safety profile in pediatric patients, including those less than 2 years of age.

It should be noted that safety reporting for this specific population is somewhat different from reporting in adult populations. Some events like nausea, warmth sensations and local pain, which are considered to be physiological adverse events to contrast media administration, sometimes cannot be reported by young patients and may not be observed by physicians. This could lead to an under-reporting of AEs in pediatric populations.

There is a potential low risk for medication errors (i.e., overdose), extravasation and vessel injury events with GBCAs. However, osmolality and viscosity of GBCAs present a lower risk in children for these types of events compared with iodinated contrast media due to smaller volumes injected and injection flow rate. Dotarem has the smallest osmolality among ionic GBCAs (MultiHance and Magnevist). Considering the low dose injected, the osmolality level is fully compatible with IV injection. The increase in plasma osmolality after injection of a 0.1 mmol/kg dose is considered insignificant (Port *et al*., 2008). The viscosity of Dotarem is compatible with IV injection and is also lower than MultiHance, Gadavist and Magnevist.

In general, due to body weight of pediatric patients less than 2 years of age, the injection volume is very small, and consequently, clinical practice cannot rely on calculated rate of injection. However, the injection should be manually controlled when administering bolus to avoid any damage to the delicate veins of children.

Although caution should be exercised in the pediatric population, no additional safety concerns have been identified in this population. Reactions most frequently reported in older age groups, such as hypersensitivity/anaphylactic reactions, have not been reported in the pediatric population.

While there are no reported cases of NSF in very young pediatric patients, caution should be used when administering any GBCAs to preterm neonates and infants due to renal immaturity and potential glomerular filtration rates under 30 mL/min/1.73 m^2 (ACR Manual on Contrast Agents, 2010).

12.4 Overall Conclusions

This application focuses on the efficacy and safety of 0.1 mmol/kg BW of Dotarem for CE-MRI of the CNS. The overall safety profile of Dotarem has been systematically characterized in clinical programs in 2813 patients exposed to Dotarem, in post-marketing observational program in more than 137,000 patients and in post-marketing experience of approximately 30 million doses administered in over 20 years of use. Since 2007, after the first NSF labeling changes were introduced outside the US, worldwide usage of Dotarem, including for pediatric patients less than 2 years of age, has increased significantly, confirming and strengthening the positive benefit/risk ratio. Numerous regulations worldwide and radiological societies such as ACR consider Dotarem as a GBCA with a low NSF risk (ACR Manual on Contrast Agents, 2010).

The potential risk for NSF after receiving Dotarem appears to be very low, maintaining a positive benefit/risk assessment for patients with severe renal impairment. Dotarem will be particularly beneficial to US patients with severe renal impairment or pediatric patients less than 2 years of age.

Accumulated safety data in pediatric patients are in line with what is currently known in the adult population. Approval of Dotarem for pediatric population use has been granted in European countries, with no increase in reported adverse reactions. New techniques utilizing gadolinium-based contrast agents are improving diagnosis. Continued development of sophisticated imaging sequences will provide faster and better examinations in the pediatric patient population. In the US, gadolinium contrast agents are currently approved for IV use in the patients over 2 years of age, but off-label applications are frequently utilized in pediatric patients less than 2 years of age.

Approval of Dotarem for intravenous use with magnetic resonance imaging (MRI) in the brain (intracranial), spine and associated tissues in

- adults and
- pediatric patients - neonates to 17 years of age

to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity will help to guide imaging physicians to use a GBCA that is stable and has a demonstrated safety record in all patient population including the vulnerable population under 2 years of age.

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APPENDIX 1

1. List of Countries Where Dotarem is Approved

Country	Pharmaceutical Form	Approval Date
ALGERIA	VIAL	6/22/1999
ARGENTINA	PRE-FILLED SYRINGE	8/28/1996
	VIAL	7/19/1994
AUSTRALIA	VIAL	12/11/2000
	PRE-FILLED SYRINGE	8/12/2010
AUSTRIA	PRE-FILLED SYRINGE	6/17/1997
	VIAL	6/17/1997
BELGIUM	PRE-FILLED SYRINGE	5/19/1995
BOLIVIA	VIAL	10/24/1989
	VIAL	11/9/2007
BOSNIA AND HERZEGOVINA	VIAL	3/29/2004
BRAZIL	PRE-FILLED SYRINGE	8/8/2001
	VIAL	8/8/2001
CHILE	PRE-FILLED SYRINGE	9/27/1996
	VIAL	9/27/1996
CHINA	PRE-FILLED SYRINGE	12/28/1998
	VIAL	12/28/1998
COLOMBIA	VIAL	5/11/1998
COSTA RICA	VIAL	1/30/2008
COTE D'IVOIRE	VIAL	12/15/2009
CROATIA	VIAL	7/28/2006
	PRE-FILLED SYRINGE	5/17/2010
CYPRUS	VIAL	7/31/2008
CZECH REPUBLIC	PRE-FILLED SYRINGE	12/30/1997
	VIAL	12/30/1997
DENMARK	VIAL	3/12/1996
	PRE-FILLED SYRINGE	2/4/2004
ECUADOR	VIAL	6/8/2011
EGYPT	PRE-FILLED SYRINGE	10/22/2002
	VIAL	10/22/2002
EL SALVADOR	VIAL	11/9/1999

Country	Pharmaceutical Form	Approval Date
FINLAND	PRE-FILLED SYRINGE	12/18/1995
	VIAL	12/18/1995
FRANCE	PRE-FILLED SYRINGE	2/13/1995
	VIAL	3/8/1989
GERMANY	PRE-FILLED SYRINGE	8/28/2003
	VIAL	8/28/2003
GREECE	PRE-FILLED SYRINGE	12/20/1996
	VIAL	1/9/1996
GUATEMALA	VIAL	9/8/2008
HONG KONG	PRE-FILLED SYRINGE	12/11/1996
	VIAL	12/11/1996
HUNGARY	VIAL	12/16/2003
INDIA	VIAL	3/1/2003
	PRE-FILLED SYRINGE	3/1/2003
INDONESIA	VIAL	7/13/2001
IRAN	VIAL	11/29/2005
IRAQ	VIAL	6/9/1999
IRELAND	PRE-FILLED SYRINGE	6/10/1996
	VIAL	6/10/1996
ISRAEL	PRE-FILLED SYRINGE	2/18/2003
	VIAL	9/1/1997
ITALY	PRE-FILLED SYRINGE	2/24/1999
	VIAL	4/24/1996
	PRE-FILLED SYRINGE	1/16/2004
JAPAN	PRE-FILLED SYRINGE	9/22/2000
JORDANIE	VIAL	9/21/2010
KUWAIT	VIAL	12/15/1999
LEBANON	VIAL	9/2/1997
LUXEMBOURG	PRE-FILLED SYRINGE	7/19/1995
	VIAL	7/31/1989
MALAYSIA	VIAL	2/28/2001
MEXICO	VIAL	10/16/1996
	PRE-FILLED SYRINGE	7/7/2004
MONTENEGRO	VIAL	6/2/2004
MOROCCO	VIAL	6/14/1996

Country	Pharmaceutical Form	Approval Date
NETHERLANDS	PRE-FILLED SYRINGE	11/1/1995
	VIAL	4/18/1991
NEW ZEALAND	PRE-FILLED SYRINGE	11/6/1997
	VIAL	11/6/1997
NORWAY	PRE-FILLED SYRINGE	4/14/1997
	VIAL	4/14/1997
PANAMA	VIAL	8/2/2001
PARAGUAY	VIAL	5/21/2009
PERU	VIAL	7/31/1996
PHILIPPINES	PRE-FILLED SYRINGE	10/30/2000
	VIAL	7/25/2000
PORTUGAL	PRE-FILLED SYRINGE	2/29/1996
	VIAL	7/6/1991
ROMANIA	PRE-FILLED SYRINGE	12/29/2006
	VIAL	12/29/2006
RUSSIAN FEDERATION	VIAL	9/17/1998
	PRE-FILLED SYRINGE	9/17/1998
SAUDI ARABIA	PRE-FILLED SYRINGE	1/28/2001
	VIAL	1/21/2001
SENEGAL	VIAL	10/14/2009
SERBIA	VIAL	6/2/2004
SINGAPORE	VIAL	11/25/1996
SLOVENIA	VIAL	2/25/2000
SOUTH AFRICA	PRE-FILLED SYRINGE	9/1/1997
	VIAL	9/1/1997
SOUTH KOREA	PRE-FILLED SYRINGE	6/29/1998
	VIAL	4/12/1995
SPAIN	PRE-FILLED SYRINGE	1/23/2006
	VIAL	12/9/1998
SWEDEN	PRE-FILLED SYRINGE	10/25/1995
	VIAL	10/25/1995
SWITZERLAND	VIAL	6/28/1990
	PRE-FILLED SYRINGE	11/1/1995
TAIWAN	PRE-FILLED SYRINGE	6/21/1999
	VIAL	6/21/1999

Country	Pharmaceutical Form	Approval Date
THAILAND	PRE-FILLED SYRINGE	10/14/1999
	VIAL	10/14/1999
TUNISIA	VIAL	5/31/1996
TURKEY	VIAL	3/26/1998
UNITED ARAB EMIRATES	VIAL	2/24/2010
UNITED KINGDOM	PRE-FILLED SYRINGE	10/31/1996
	VIAL	10/31/1996
URUGUAY	PRE-FILLED SYRINGE	7/1/1998
	VIAL	7/16/1998
VENEZUELA	VIAL	6/19/2002
VIETNAM	VIAL	6/3/2002

2 Approved Indications per Country

2.1 Overall

Europe

Approved indication	AT	BE	CZ	DE	DK	ES	FI	FR	IE	IT	LU	NL	NO	PT	SE	UK
CNS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole-Body	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Approved indication	GR	CY	HU	RO	SI	CH	RU	BA	HR
CNS	X	X	X	X	X	X	X	X	X
Whole-Body	X	X	X	X	X	X	X	X	X
MRA	X	X	X	X	X	X	X	X	X

Latin America

Approved indication	BR	AR	MX	CO	CL	PE	UY	VE	BO	CR	GT	PY	SV	EC	PA
CNS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole-Body	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Asia and Pacific Region

Approved indication	CN	HK	IN	KR	TW	SG	MY	ID	VN	PH	TH	NP	AU	NZ	JP
CNS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole-Body	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Middle East and Africa

Approved indication	IL	TR	MA	TN	DZ	LB	EG	SA	KW	JO	IR	IQ	AE	SN	CI	CM	ZA
CNS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole-Body	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

2.2 Pediatric Patients

Approved indications for pediatric categories for CNS and whole body indication per country.

Europe

Approved class of age	AU	BE	CZ	DE	DK	ES	FI	FR	IE	IT	LU	NL	NO	PT	SE	UK
0-4 weeks	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
1-12 months	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
1-2 years	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
2-18 years	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Approved class of age	GR	CY	HU	RO	SI	CH	RU	BA	HR
0-4 weeks	X	X	X	X	X	X	X	X	X
1-12 months	X	X	X	X	X	X	X	X	X
1-2 years	X	X	X	X	X	X	X	X	X
2-18 years	X	X	X	X	X	X	X	X	X

Latin America

Approved class of age	BR	AR	MX	CO	CL	PE	UY	VE	BO	CR	GT	PY	SV	EC	PA
0-4 weeks	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
1-12 months	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
1-2 years	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2-18 years	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Asia and Pacific Region

Approved class of age	CN	HK	IN	KR	TW	SG	MY	ID	VN	PH	TH	NP	AU	NZ	JP
0-4 weeks	X	X	X	X	X		X	X	X	X	X	X	X	X	
1-12 months	X	X	X	X	X		X	X	X	X	X	X	X	X	
1-2 years	X	X	X	X	X		X	X	X	X	X	X	X	X	
2-18 years	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Middle East and Africa

Approved class of age	IL	TR	MA	TN	DZ	LB	EG	SA	KW	JO	IR	IQ	AE	SN	CI	CM	ZA
0-4 weeks	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
1-12 months	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
1-2 years	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2-18 years	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Glossary

Country Code	Country	Country Code	Country
AE	United Arab Emirates	IR	Iran
AR	Argentina	IT	Italy
AT	Austria	JO	Jordan
AU	Australia	JP	Japan
BA	Bosnia and Herzegovina	KR	South Korea
BE	Belgium	KW	Kuwait
BG	Bulgaria	LB	Lebanon
BO	Bolivia	LU	Luxembourg
BR	Brazil	MA	Morocco
CH	Switzerland	MX	Mexico
CI	Côte d'Ivoire	MY	Malaysia
CL	Chile	NL	Netherlands
CM	Cameroon	NO	Norway
CN	China	NP	Nepal
CO	Colombia	NZ	New Zealand
CR	Costa Rica	PA	Panama
CY	Cyprus	PE	Peru
CZ	Czech Republic	PH	Philippines
DE	Germany	PT	Portugal
DK	Denmark	PY	Paraguay
DZ	Algeria	RO	Romania
EC	Ecuador	RU	Russian Federation
EG	Egypt	SA	Saudi Arabia
ES	Spain	SE	Sweden
FI	Finland	SG	Singapore
FR	France	SI	Slovenia
UK	United Kingdom	SN	Senegal
GR	Greece	SV	El Salvador
HK	Hong Kong	TH	Thailand
HR	Croatia	TN	Tunisia
HU	Hungary	TR	Turkey
ID	Indonesia	TW	Taiwan
IE	Ireland	UY	Uruguay
IL	Israel	VE	Venezuela
IN	India	VN	Viet Nam
IQ	Iraq	ZA	South Africa

APPENDIX 2

Studies Conducted by Guerbet for the Efficacy and/or Safety Evaluation of Dotarem

Author Year Study	Imaging Indication	Study Design Type of Subjects	Number of Subjects*	Dose of Dotarem (mmol/kg)	Clinical Monitoring/ Lab Tests	VAS of Patient Discomfort
CNS INDICATION						
Pruvo 2003 DGD 3-44	CNS	NR, O, M, C	150	0.1	BP, HR, RR	Yes
No coordinator 2010 DGD 44-050	CNS	R, DB, M, C Patients	278	0.1	ECG, BP, HR, Lab test	Yes
Caille 1987 DGD 3-7	CNS	O, NR Patients	56	0.1	No	Yes
Caille 1987 DGD 3-11	CNS	O, NR Patients	19	0.1	EEG and, Lab test	Yes
Doyon 1987 DGD 3-4	CNS	O, NR Patients	20	0.1	Lab test	Yes
Doyon 1987 DGD 3-8	CNS	O, NR Patients	54	0.1	No	Yes
Metzger 1987 DGD 3-1	CNS	O, NR Patients	10	0.1	Lab test	Yes
Simon 1987 DGD 3-12	CNS	O, NR Patients	50	0.1	No	Yes
Simon 1987 DGD 3-14	CNS	O, NR Patients	55	0.1	No	Yes
Caille 1988 DGD 3-23	CNS	O, NR Patients	50	0.1	No	No
Cornelis 1988 DGD 3-5	CNS	O, NR Patients	10	0.1	Lab test	Yes
De Schepper 1988 DGD 3-9	CNS	O, NR Patients	22	0.1	Lab test	No

Abbreviations: BP = blood pressure; CNS = central nervous system; DB = double blind; ECG = electrocardiogram; Gd-DTPA = gadopentatate dimeglumine (Magnevist); HR = heart rate; M = multicenter; NR = not randomized; O = open label; PG = parallel groups; PK = pharmacokinetics; R = randomized; RR = respiratory rate; S = single center; VAS = Visual Analog Scale

* Safety population

Studies Conducted by Guerbet for the Efficacy and/or Safety Evaluation of Dotarem

Author Year Study	Imaging Indication	Study Design Type of Subjects	Number of Subjects*	Dose of Dotarem (mmol/kg)	Clinical Monitoring/ Lab Tests	VAS of Patient Discomfort
Gandon 1988 DGD 3-16	CNS	O, NR Children	20	0.1	No	No
Lallemand 1988 DGD 3-15	CNS	O, NR Children	29	0.1	Lab test	No
Manelfe 1988 DGD 3-17	CNS	R, DB, PG Gd-DTPA Patients	10	0.1	Lab test	No
Manelfe 1988 DGD 3-3	CNS	O, NR Patients	30	0.1	Lab test	Yes
Manelfe 1988 DGD 3-21	CNS	O, NR Patients	50	0.1	No	Yes
Vignaud 1988 DGD 3-20	CNS	O, NR Patients	48	0.1	No	Yes
Brugières 1990 DGD 3-31	CNS	R, DB, PG Gd-DTPA Patients	149	0.1	No	No
Pariente 1991 DGD 3-29	CNS	O, NR Children	50	0.1	No	No
Caille 1994 DGD 3-34	CNS	O, NR Patients	45	0.3	Lab test	No
Salamon 1994 DGD 3-33	CNS	O, NR Patients	65	0.3	No	No
Marsault 2000 DGD 3-40	CNS	O, NR Patients	59	0.2	No	No
PHARMACOKINETIC / ECG STUDIES						
Le Mignon 1990 DGD 3-6	PK	O, NR Healthy Volunteers	6	0.1	ECG, BP, HR, Lab test	No
Chachuat 1992 DGD 3-28	PK	O, NR Healthy Volunteers / Renal failure Patients	12	0.1	ECG, BP, HR, Lab test	No

Abbreviations: BP = blood pressure; CNS = central nervous system; DB = double blind; ECG = electrocardiogram; Gd-DTPA = gadopentatate dimeglumine (Magnevist); HR = heart rate; M = multicenter; NR = not randomized; O = open label; PG = parallel groups; PK = pharmacokinetics; R = randomized; RR = respiratory rate; S = single center; VAS = Visual Analog Scale

* Safety population

Studies Conducted by Guerbet for the Efficacy and/or Safety Evaluation of Dotarem

Author Year Study	Imaging Indication	Study Design Type of Subjects	Number of Subjects*	Dose of Dotarem (mmol/kg)	Clinical Monitoring/ Lab Tests	VAS of Patient Discomfort
Chassard 2004 DGD 3-48	PK	O, NR Healthy Volunteers	32	0.1 - 0.3	ECG, BP, HR, Lab test	No
Fauchoux 2003 DGD 44-039	ECG	O, R Patients	40	0.1 - 0.3	ECGs BP, HR, Lab test	Yes
OTHER INDICATIONS						
Bigot 1988 DGD 3-22	Liver/Pancreas	O, NR Patients	24	0.1	No	Yes
Drouillard 1988 DGD 3-13	Liver/Pancreas	O, NR Patients	30	0.1 - 0.2	No	No
Grellet 1991 DGD 3-19	Liver/Pancreas	O, NR Patients	39	0.1 - 0.2	No	Yes
Vanel 1988 DGD 3-2	Musculoskeletal	O, NR Patients	20	0.1	Lab test	Yes
Bellin 1992 DGD 3-26	Kidney	O, R, PG Renal impaired patients	10	0.2	Lab test	No
Vanel 1994 DGD 3-32	Breast	O, NR Patients	80	0.1	No	No
Vilgrain 2007 DGD 3-49	Whole-body	O, NR, M, C Patients	120	0.1	BP, HR, RR	Yes
Roy 2007 DGD 3-50	Whole-body	O, NR, M, C Renal impaired patients	109	0.1	BP, HR, RR	Yes
Deray 2008 DGD 44- 044	Whole-body	O, NR, M, C Patients	70	0.1	BP, HR, Lab test	No
Douek 1998 DGD 3-36	MRA/renal artery	O, NR Patients	41	0.1	No	No
Marchal 1998 DGD 3-38	MRA/carotid artery	O, NR Patients	40	0.1	No	No

Abbreviations: BP = blood pressure; CNS = central nervous system; DB = double blind; ECG = electrocardiogram; Gd-DTPA = gadopentatate dimeglumine (Magnevist); HR = heart rate; M = multicenter; NR = not randomized; O = open label; PG = parallel groups; PK = pharmacokinetics; R = randomized; RR = respiratory rate; S = single center; VAS = Visual Analog Scale

* Safety population

Studies Conducted by Guerbet for the Efficacy and/or Safety Evaluation of Dotarem

Author Year Study	Imaging Indication	Study Design Type of Subjects	Number of Subjects*	Dose of Dotarem (mmol/kg)	Clinical Monitoring/ Lab Tests	VAS of Patient Discomfort
Laissy 1998 DGD 3-39	MRA/lower limb artery	O, NR Patients	40	0.1 - 0.2	No	No
Oudkerk 1998 DGD 3-37	MRA/pulmonary embolism	O, NR Patients	35	0.1 - 0.2	No	No
Oudkerk 2004 DGD 3-42	MRA/ coronary artery stenosis	O, NR Patients	6	0.125 – 0.25	No	No
Wolf 2006 DGD 44-38	MRA/ non coronary artery stenosis	O, NR Patients	100	0.1	BP, HR	No
Lim 2008 DGD 44-42	MRA/ non coronary artery stenosis	O, NR Patients	92	0.1	BP, HR	No
No coordinator 2009 DGD 44- 046	MRA/renal artery	O, NR, M Patients	32	0.1	BP, RR Lab test	Yes
No coordinator 2009 DGD 44-047	MRA/renal artery	O, NR, M Patients	10	0.1	BP, RR Lab test	Yes
No coordinator 2009 DGD 44-048	MRA/Carotid and vertebral	O, NR, M Patients	200	0.1	BP, RR Lab test	Yes
No coordinator 2009 DGD 44-049	MRA/Carotid and vertebral	O, NR, M Patients	187	0.1	BP, RR Lab test	Yes
Michaely 2009 DGD 44-052	MRA	DB, R, S, C Patients	17	0.1	BP, HR	Yes
Loewe 2010 DGD 44-045	MRA	DB, R, M, C Patients	92	0.1	BP, RR	Yes
Total number of patients			2813			

Abbreviations: BP = blood pressure; CNS = central nervous system; DB = double blind; ECG = electrocardiogram; Gd-DTPA = gadopentatate dimeglumine (Magnevist); HR = heart rate; M = multicenter; NR = not randomized; O = open label; PG = parallel groups; PK = pharmacokinetics; R = randomized; RR = respiratory rate; S = single center; VAS = Visual Analog Scale

* Safety population

APPENDIX 3:

Laboratory Parameter Results for Clinical Studies

Study	Total Number of Dotarem treated Patients	Imaging Indication	Hematology	Biochemistry	Results
DGD-44-050	278	CNS	T0, T0 + 24(±4)h	T0, T0 + 24(±4)h	No clinically relevant trends in mean hematology/biochemistry laboratory parameters were apparent in adult patients and no pediatric patients had clinically significant changes.
DGD-44-049	187	MRA	T0, T0 + 24(±4)h	T0, T0 + 24 (±4)h	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.
DGD-44-048	200	MRA	T0, T0 + 24(±4) h	T0, T0 + 24(±4)h	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.
DGD-44-047	10	MRA	T0, T0 + 24(±4)h	T0, T0 + 24(±4) h	No clinically significant laboratory abnormalities occurred.
DGD-44-046	32	MRA	T0, T0 + 24(±4)h	T0, T0 + 24(±4)h	3 patients had biochemistry abnormalities
					1 patient had hematological abnormalities
					None of these events were considered related to study treatment.
DGD-44-044	70	Various	T0, T0 + 72 h	T0,T0 + 72 h	Considering population included (patients with chronic renal failure) 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 (with or without Dotarem) , 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.
DGD-44-039	40	Cardiac disorders	T0, T0 + 24h	T0, T0 + 24h	There were no relevant changes from baseline in any laboratory parameters assessed.
DGD-3-1	10	CNS	ND	T0, T0 + 2 h, T0 + 24 h	No significant variation in parameters observed apart from blood glucose (at 2 hours, this variation was very moderate and attributable to postprandial values).

Abbreviations: CNS = central nervous system; MRA = magnetic resonance angiography; ND = not done; PK = pharmacokinetics; T0 = before injection

Laboratory Parameter Results for Clinical Studies

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

Abbreviations: CNS = central nervous system; MRA = magnetic resonance angiography; ND = not done; PK = pharmacokinetics; T0 = before injection

Summary of Vital Signs and Changes Relative to Baseline in Adult Patients (Study DGD-44-050)

	Time after Injection N = 357					
	5 minutes		15 minutes		24 hours	
	Dotarem	Magnevist	Dotarem	Magnevist	Dotarem	Magnevist
Systolic blood pressure (mm Hg)						
Mean						
N	239	117	238	117	238	117
Mean	127.12	130.30	127.52	130.84	124.18	126.63
SD	19.02	24.90	18.31	26.58	16.62	16.34
Change						
Mean	0.41	-1.03	0.82	-0.49	-2.31	-4.69
SD	9.70	7.82	9.56	8.83	16.78	19.96
Clinical range						
<-20	1 (0.4%)	1 (0.9%)	3 (1.3%)	1 (0.9%)	24 (10.1%)	12 (10.3%)
[-20 . +30]	235 (98.3%)	116 (99.1%)	233 (97.9%)	116 (99.1%)	209 (87.8%)	104 (88.9%)
>30	3 (1.3%)	0	2 (0.8%)	0	5 (2.1%)	1 (0.9%)
Diastolic blood pressure (mm Hg)						
Mean						
N	239	117	238	117	238	117
Mean	77.97	78.53	78.13	79.18	77.05	76.84
SD	12.45	11.68	11.78	13.13	10.45	10.56
Change						
Mean	0.10	-0.56	0.26	0.09	-0.53	-2.25
SD	6.96	8.11	7.46	9.13	11.50	11.07
Clinical range						
<-20	5 (2.1%)	4 (3.4%)	8 (3.4%)	2 (1.7%)	17 (7.1%)	13 (11.1%)
[-20 . +30]	232 (97.1%)	113 (96.6%)	228 (95.8%)	113 (96.6%)	212 (89.1%)	104 (88.9%)
>30	2 (0.8%)	0	2 (0.8%)	2 (1.7%)	9 (3.8%)	0
Heart rate (bpm)						
Mean						
N	238	117	237	117	236	117
Mean	73.79	74.11	73.25	73.93	74.51	75.21
SD	14.34	13.15	13.03	13.23	11.89	13.51

Abbreviations: bpm: beats per minute; SD: standard deviation
Source: Clinical Study Report DGD-44-050 Table 12.5-1

Summary of Vital Signs and Changes Relative to Baseline in Adult Patients (Study DGD-44-050)

	Time after Injection N = 357					
	5 minutes		15 minutes		24 hours	
	Dotarem	Magnevist	Dotarem	Magnevist	Dotarem	Magnevist
Change						
Mean	0.79	0.16	0.24	-0.02	1.66	1.26
SD	5.75	5.88	7.06	6.92	11.54	13.51
Clinical range						
<-20	0	2 (1.7%)	3 (1.3%)	2 (1.7%)	10 (4.2%)	6 (5.1%)
[-20 . +30]	233 (97.9%)	115 (98.3%)	231 (97.5%)	115 (98.3%)	214 (90.7%)	105 (89.7%)
>30	5 (2.1%)	0	3 (1.3%)	0	12 (5.1%)	6 (5.1%)

Abbreviations: bpm: beats per minute; SD: standard deviation
Source: Clinical Study Report DGD-44-050 Table 12.5-1

Summary of Vital Signs and Changes Relative to Baseline in Pediatric Patients (Study DGD-44-050)

	Time after injection		
	5 minutes N=38	15 minutes N=38	24 hours N=38
Systolic blood pressure (mmHg)			
Mean			
N	38	38	35
Mean	92.24	96.63	103.14
SD	16.12	17.82	13.07
Change			
Mean	-0.11	4.29	9.43
SD	4.32	10.18	13.56
Clinical range			
<-20	0	0	2 (5.3%)
[-20 +30]	38 (100.0%)	37 (97.4%)	32 (84.2%)
>30	0	1 (2.6%)	1 (2.6%)
Diastolic blood pressure (mmHg)			
Mean			
N	38	38	35
Mean	52.32	56.05	63.26
SD	14.55	14.63	10.67

Abbreviations: bpm: beats per minute; SD: standard deviation
Source: Clinical Study Report DGD-44-050 Table 12.5-2

Summary of Vital Signs and Changes Relative to Baseline in Pediatric Patients (Study DGD-44-050)

	Time after injection		
	5 minutes N=38	**15 minutes N=38**	**24 hours N=38**
Change			
Mean	-0.89	2.84	8.80
SD	3.57	6.87	16.32
Clinical range			
<-20	0	1 (2.6%)	2 (5.3%)
[-20 . +30]	38 (100.0%)	37 (97.4%)	23 (60.5%)
>30	0	0	10 (26.3%)
Heart rate (bpm)			
Mean			
N	38	38	35
Mean	87.13	89.61	90.43
SD	17.30	20.69	14.48
Change			
Mean	-0.50	1.97	5.49
SD	4.09	10.28	12.61
Clinical range			
<-20	0	0	0
[-20 +30]	38 (100.0%)	36 (94.7%)	30 (78.9%)
>30	0	2 (5.3%)	5 (13.2%)

Abbreviations: bpm: beats per minute; SD: standard deviation
Source: Clinical Study Report DGD-44-050 Table 12.5-2