CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204781Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 8, 2013
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	204781
Applicant Name	Guerbet, LLC
Date of Submission	September 20, 2012
PDUFA Goal Date	March 20, 2013
Proprietary Name / Established (USAN) Name	Dotarem/gadoterate dimeglumine
Dosage Forms / Strength	A solution for intravenous injection/supplied in vials, prefilled syringes and as a pharmacy bulk package; all presentations contain 376.9 mg/mL gadoterate dimeglumine.
Proposed Indication(s)	"Dotarem is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity."
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Barbara Stinson, MD
Statistical Review	Satish Misra, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Olayinka Dina, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Milagros Salazar Driver, PhD & Eldon Leutzinger, PhD (TL)
Microbiology Review	Vinayak Pawar, PhD
Clinical Pharmacology Review	Christy John, PhD & Y. Gene Williams, PhD (TL)
DDMAC/DPDP	James Dvorsky
DSI	John Lee, MD
CDTL Review	Alex Gorovets, MD
OSE/DMEPA	Kevin Wright, PharmD & Yelena Maslov, PharmD (TL)
OSE/DPV II	Michael Kieffer, PharmD & Joseph Tonning, MD & Peter Diak, PharmD (TL)
Pediatric and Maternal Health	Erica Radden, MD
Project Manager	James Moore, PharmD

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication renamed as DPDP, Division of Professional Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls
DPV = Division of Pharmacovigilance II

1. Introduction:

This document summarizes the basis for approval of Dotarem for use in patients aged two years or more, consistent with agreed-upon labeling and pending resolution of any establishment inspectional issues. Dotarem will be supplied in single dose vials, pre-filled syringes and a pharmacy bulk package.

This first cycle submission was intended to support the approval of Dotarem (FDA-accepted proprietary name) for use in central nervous system (CNS) magnetic resonance imaging (MRI) of all patients, including infants. If approved, Dotarem will be the ninth gadolinium-based contrast agent (GBCA) approved by the FDA. None of the currently approved GBCAs are approved for use in patients aged less than two years, so the Dotarem application was especially notable for its proposed use in infants. This unique pediatric proposal prompted a discussion at a Medical Imaging Drugs Advisory Committee (MIDAC) on February 14, 2013.

The MIDAC advisors overwhelmingly supported a favorable safety/efficacy finding for Dotarem's use among patients aged two years or more, but the committee did not regard the supplied data as sufficient to support approval of the drug for use in patients aged less than two years. Specifically cited data deficits were for a non-clinical toxicology study in juvenile animals and the lack of clinical pharmacology data from patients aged less than two years. Subsequent discussions within the review team culminated in a recommendation for approval of Dotarem to include an indication statement that confined use of the drug to patients aged two years or more. I support this recommendation for approval of the drug in patients aged two years or more. Post-marketing requirements will address the need for data from a juvenile animal model study and a clinical pharmacology study of patients aged less than two years.

All recommendations for approval are contingent upon the findings from establishment inspections—the Office of Compliance has not completed its review of this application on the 21st century timeline; hence, this review is pending and the findings (mainly of establishment inspectional status) may importantly impact the final NDA review status.

The sponsor's main phase 3 trial robustly demonstrated the added value of Dotarem to non-contrasted MRI and a "reread" clinical study also supported the drug's efficacy. The NDA database did not identify any safety considerations that had not been previously identified for a GBCA. As a member of the class of GBCA drugs, Dotarem labeling will carry the same class-wide warning for nephrogenic systemic fibrosis (NSF).

Dotarem has been marketed outside the United States for approximately two decades; to date no "unconfounded" cases of NSF have been attributed to Dotarem. An "unconfounded" case is a report of a patient who developed NSF following exposure only to Dotarem. NSF reports have cited situations where a patient received multiple GBCAs (such as Magnevist, Omniscan, etc.)—such that these reports are regarded as "confounded" by the relatively complex drug exposure history.

2. Background:

GBCAs are paramagnetic MRI contrast agents used to improve the visualization of body structures or vasculature. To date, FDA has approved eight GBCAs (six for a CNS indication, see Table 1). The agents contain gadolinium, a paramagnetic metal which must remain chelated within the agent to avoid toxic effects from the gadolinium.

Table 1. Dotarem and Currently Approved GBCAs

Trade name	Established name	Indication	Dose, adult mmol/kg	Molar	Chemical structure
Magnevist	gadopentetate dimeglumine	CNS, body	0.1	0.5	Linear, ionic
Prohance	gadoteridol	CNS	0.1	0.5	Macrocyclic
Omniscan	gadodiamide	CNS, body	0.1	0.5	Linear, non-ionic
Optimark	gadoversetamide	CNS, liver	0.1	0.5	Linear, non-ionic
Multihance	gadobenate dimeglumine	CNS	0.1	0.5	Linear, ionic
Eovist	gadoxetate	Liver	0.025	0.25	Linear, ionic
Ablavar	gadofosveset	Aorto-iliac vessels	0.03	0.25	Linear, ionic
Gadavist	Gadobutrol	CNS	0.1	1.0	Macrocyclic
Pending	Gadoterate dimegluming	CNS	0.1	0.5	Macrocyclic

GBCAs are widely acknowledged as critical to optimal MRI visualization of many parts of the body and are regarded as particularly valuable for tumor detection/anatomical characterization. To date, the predominant safety concerns have related to hypersensitivity reactions (anaphylactoid reactions, some fatal) and an association with nephrogenic systemic fibrosis (NSF).

In 2006 NSF, a scleroderma-like disease was associated with the use of GBCAs among patients with severe renal insufficiency. NSF produces characteristic skin lesions and a fibrotic process within multiple body organs which may result in death. There is no generally accepted treatment or cure. FDA and drug manufacturers have extensively modified labeling over the past four years in order to help minimize the NSF risk. These actions, as discussed at a December 2009 FDA advisory committee, have been credited with helping to reduce the occurrence of the condition since the initial reports surfaced in

2006/2007. In general, the reduction has been proposed to be related to enhanced screening for renal dysfunction and more judicious use of the agents.

In December, 2010, FDA approved revisions of GBCA labels to distinguish two major subsets of GBCAs: a group that is contraindicated for use among the highest risk patient population and a group that lacks this contraindication. The labeling change emphasized some magnitude of NSF risk for all the GBCAs in the vulnerable population (especially patients with severe, chronic kidney disease or acute kidney injury, the highest risk population). Consequently, all members of the GBCA class are anticipated to contain NSF risk information.

As shown in Table 1, Dotarem has a "macrocyclic" structure which has been proposed to reduce the risk for liberation of gadolinium from the chelate and potentially lessen the risk for NSF, in comparison to other GBCAs. These concepts have not been verified and the relative importance of chemical structure in defining the NSF risk has not been established in comparison to other risk covariates (such as the extent of underlying kidney disease or agent dose).

Although the GBCA are viewed as a "class" based upon the same pharmacologic mechanism of action, the agents uniquely differ in multiple aspects (e.g., pharmacokinetics, pharmaco-dynamics, chemical structure, chelate-ion binding characteristics, etc). In this regard, FDA-approved labeling based upon a "GBCA class effect" did not mean that all GBCAs have identical risks and benefits nor did it mean that the magnitude of any individual risk (e.g., NSF) was the same for all members of the class. Instead, the NSF "class" risk indicated that the potential for the risk exists among all members of the drug class.

The Dotarem sponsor estimated that approximately 30 million people have received Dotarem during its marketing outside the United States. The paucity of NSF reports associated with exposure to Dotarem (no "unconfounded" reports) justifies labeling for Dotarem that does not carry a contraindication pertaining to the NSF risk. Overall, the supplied data support the approval of Dotarem in patients aged two years or more.

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed by Dr. Milagros Salazar Driver who reviewed the applicant's supplied manufacturing information. Dr Salazar Driver also coordinated the review of the syringe (consultation with reviewers in the Center for Devices and Radiological Health). Dr. Salazar Driver confirms that manufacturing issues have been resolved, exclusive of facility inspections and a last moment request to the sponsor (pertaining expiry times). Facility inspection report development is ongoing and, at the time of this report, the core review team has not received an update from the Office of Compliance regarding the nature of any inspectional findings. The Compliance reviewers have promised the team that a report will be generated prior to the PDUFA due date. Dr. Salazar Driver has recently sent a request to the NDA sponsor to update the

expiry time for their presentations; the review team anticipates that the sponsor will promptly update the NDA but this response is pending.

Dr. Salazar Driver has not identified a need for post-marketing studies. I concur with her observations and tentative conclusions.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. Olayinka Dina who found the supplied nonclinical pharmacology/toxicology data supportive of the drug's approval. CNS safety in conscious animals showed no important safety concerns for clinically relevant Dotarem doses. Cardiovascular safety was confirmed in dogs by the establishment of a no-adverse-effect level of more than three times the clinically applicable dose. Similarly, no unique respiratory or renal safety signals were identified in animal studies. Animal pharmacokinetic studies verified that Dotarem is excreted almost entirely by the kidneys.

Single dose and repeated dose toxicology studies revealed no concerning safety findings; the single dose NOAEL in dogs was 14-fold higher than the clinically applicable Dotarem dose.

Gadoterate meglumine was not mutagenic in the Ames test, chromosomal aberration test and an *in vivo* micronucleus test. No carcinogenicity studies were conducted (as typical for contrast agents).

Reproductive and developmental toxicity studies were conducted with gadoterate meglumine in rats and rabbits. No effects on embryo fetal development were observed in rats or rabbits at doses of 10 mmol/kg/day in rats or 3 mmol/kg/day in rabbits. Maternal toxicity was observed in rats at 10 mmol/kg/day (or 16 times the human dose based on body surface area) and in rabbits at 7 mmol/kg/day (23 times the human dose based on body surface area). No impairment of male or female fertility and reproductive performance was observed in rats after intravenous administration of gadoterate meglumine at the maximum tested dose of 10 mmol/kg/day (16 times the maximum human dose based on surface area), given during more than 9 weeks in males and more than 4 weeks in females. Sperm counts and sperm motility were not adversely affected by treatment with the drug.

Local intolerance reactions, including moderate irritation associated with infiltration of inflammatory cells was observed after subcutaneous or intramuscular injection in rats and after intravenous, intra-arterial or perivenous injection in rabbits.

Two potential impurities were found to have no important safety findings following toxicity study evaluations.

Because the NDA sponsor was proposing use of Dotarem among infants, the review team regarded a toxicology study in juvenile animals as essential to identify safety signals (which might impact labeling as well as post-marketing studies). The NDA sponsor did not submit results from a juvenile animal study; the sponsor has apparently been working

to complete the study and, at the advisory committee meeting, the sponsor stated the results should be available by the end of 2013.

5. Clinical Pharmacology/Biopharmaceutics:

I have read the review performed by Dr. Christy John and I concur with his recommendations. Dr. John noted that the NDA sponsor performed four clinical pharmacology studies, including one study that enrolled patients with various degrees of renal impairment and one study that assessed gadoterate effects on EKG QTc intervals.

The clinical pharmacology findings for gadoterate appeared typical for a GBCA with excretion almost entirely by the kidneys; hence, the drug may be associated with extended patient exposure in the setting of renal impairment. The clinical pharmacology team noted a lack of clinical pharmacology data for pediatric patients—a finding which is especially important since the NDA sponsor had requested approval of the drug for use in infants. The clinical pharmacology team's request for clinical pharmacology data in infants was supported by the MIDAC and this request is culminating in a post-marketing requirement.

With respect to potential EKG effects, gadoterate was shown to have no effect on QTc intervals in a clinical pharmacology study.

6. Clinical Microbiology:

Dr. Vinayak Pawar completed the review of the applicant's microbiology-related information; he detected no deficiencies and I concur with his findings. No post-marketing studies were proposed.

7. Clinical/Statistical-Efficacy:

Dr. Barbara Stinson performed the primary clinical review and presented the clinical data at the MIDAC. Dr. Alex Gorovets performed the Cross Discipline Team Leader review. Dr. Satish Misra performed the statistical review. I have read the reviews and concur with the findings.

The NDA sponsor provided data from a single phase 3 clinical trial that robustly demonstrated the value of Dotarem in CNS imaging. The clinical data's limitations were confined to the pediatric population where Dr. Stinson noted that only seven patients aged less than two years had been evaluated following Dotarem administration—and no pediatric patients provided clinical pharmacology data. The paucity of data (non-clinical juvenile animal and clinical pharmacology) forms the basis for not recommending approval of Dotarem for use in patients aged less than two years. Below I excerpt the main efficacy findings from the draft labeling.

Efficacy and safety of Dotarem were evaluated in a multi-center clinical trial (Study A) that enrolled 364 adult and 38 pediatric patients (aged ≥ 2 years) with known or

suspected CNS lesions. Adults were randomized 2 to 1 to receive either Dotarem or gadopentetate dimeglumine, each administered at a dose of 0.1 mmol/kg. All pediatric patients received Dotarem, also at a dose of 0.1 mmol/kg. In the trial, patients first underwent a baseline (pre-contrast) MRI examination followed by the assigned GBCA administration and a post-contrast MR examination. The images (pre-contrast, post-contrast and "paired pre- and post-contrast") were interpreted by three independent off-site readers blinded to clinical information. The primary efficacy analysis compared three patient-level visualization scores (paired images) to baseline MRI (pre-contrast images) for adults who received Dotarem. The three primary visualization components were: contrast enhancement, border delineation and internal morphology. For each of these components there was a pre-defined scoring scale. Lesion counting (up to five per patient) was also reflected within each component's patient level visualization score.

Among the adult patients, 245 received Dotarem and their data comprised the primary efficacy population. There were 114 (47%) men and 131 (53%) women with a mean age of 53 years (range 18 to 85 years), the racial and ethnic representations were 84% Caucasian, 11% Asian, 4% Black, and 1% other.

The following table displays a comparison of paired images (pre-and post-contrast) to pre-contrast images with respect to the proportion of patients who had paired image scores that were greater "better," or same/worse "not better" than the pre-contrast scores and with respect to the difference in the mean patient level visualization score . Across the three readers 56% to 94% of patients had improved lesion visualization for paired images compared to pre-contrast images. Dotarem provided a statistically significant improvement for all three primary visualization components. More lesions were seen on the paired images than the pre-contrast images.

Study A. Improvement in Patient-level Lesion Visualization Scores, Paired versus Pre-contrast Images[(a)]

Lesion Scores	Reader 1	Reader 2	Reader 3
	n = 231	n = 232	n = 237
Border Delineation			
Better	195 (84%)	215 (93%)	132 (56%)
Not Better	28 (12%)	7 (3%)	88 (37%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [(b)]	2.26*	2.89*	1.17*
Internal Morphology			
Better	218 (94%)	214 (93%)	187 (79%)
Not Better	5 (2%)	8 (3%)	33 (14%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [(b)]	2.74*	2.75*	1.54*
Contrast Enhancement			
Better	208 (90%)	216 (93%)	208 (88%)
Not Better	15 (6%)	6 (3%)	12 (5%)
Missing	8 (4%)	10 (4%)	17 (7%)

Difference in Mean Score [(b)]	3.09*	3.69*	2.92*

(a) Better: number of patients with paired (pre- and post-contrast) score greater than the pre-contrast score
Not better: number of patients with paired score same as or worse than the pre-contrast score
Missing: number of patients with missing score.
(b) Difference = paired mean score minus pre-contrast mean score
*Statistically significant improvement by paired t-test

In secondary analyses, post-contrast images were improved in comparison to pre-contrast images. Dotarem lesion visualization scores were similar to those for gadopentetate meglumine. Dotarem imaging results in the pediatric patients were also similar to those seen in adults.

In a second clinical trial (Study B), MR images were reread from 150 adult patients with known CNS lesions who had participated in previously conducted clinical trial. Dotarem administration and image interpretation was performed in the same manner as in Study A. Similar to Study A, this trial also demonstrated improved lesion visualization with Dotarem.

8. Safety:

Based upon the clinical trial exposure of 2813 patients, the reactions to Dotarem appear typical for a GBCA. The most common reactions (all occurring in less than 1% of patients) were nausea and headache. Postmarketing reactions were notable for reports of hypersensitivity reactions, including fatal reactions, as well as some reports of worsening renal function following Dotarem administration. These reactions were isolated, very uncommon reports from an exposure population estimated in the millions and appear in a pattern similar to that of other GBCAs. No "unconfounded" reports of NSF have appeared following Dotarem administration.

Post-marketing Requirements (PMR):
The PMR pertain to the need for additional information to support use of Dotarem among patients aged less than two years:

-a juvenile animal model study

-a study conducted among patients less than two years of age; patients undergoing MRI will have blood analyzed for pharmacokinetics; safety outcomes will also be assessed; the review team discussed urine collection with the NDA sponsor; the sponsor preferred blood sampling based upon feedback from pediatric consultants. The review team regarded efficacy (for patients aged less than two years) as sufficiently extrapolated from the adult and older pediatric patient experience.

Post-marketing Commitments (PMC): none

9. Advisory Committee Meeting:

Dotarem was the subject of a meeting of the Medical Imaging Advisory Committee (MIDAC) held on February 14, 2013. In this meeting, the committee discussed the safety and efficacy of Dotarem for the proposed indication, and whether the "risk to benefit" assessment of Dotarem is favorable for use in MRI, particularly for pediatric patients aged younger than two years of age. The committee voted unanimously that Dotarem demonstrated efficacy for all patient groups and that the risk to benefit assessment is favorable for adults and pediatric patients aged two years of age and older. In a 6-10-1 vote (yes-no-abstention), the committee voted against approval of Dotarem for pediatric patients aged younger than two years of age due to lack of clinical and pharmacokinetic data in this age group as well as lack of juvenile animal toxicology data.

10. Pediatrics:

The PERC agreed with the planned deferral of the required PMRs pertaining to use of Dotarem among patients aged less than two years. The specific timeline for the completion of the PMRs is currently pending, based upon on-going discussions with the NDA sponsor. The Pediatric/Maternal Health Team review document is currently pending but representatives have been engaged throughout this review period.

11. Other Relevant Regulatory Issues:

Dr. Lee's review documents no notable deficiencies from inspection of the clinical data obtained from targeted clinical sites (as well as the sponsor and contract research organization) involved in the phase 3 trials.

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/s/

RAFEL D RIEVES
03/08/2013