CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204781Orig1s000

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging Products

Application Number: NDA 204-781

Name of Drug: DOTAREM® (Gadoterate meglumine) 376.9mg/mL/0.5mmol/mL Injection

Applicant: Guerbet

Date: March 20, 2013

Material Reviewed:

Submission Date: September 20, 2012, March 8, 18, 2013

Receipt Date: September 20, 2012, March 8, 18, 2013

Submission Date of Structure Product Labeling (SPL): September 20, 2012

Type of Labeling Reviewed: Word/SPL/Carton/Container

Background and Summary

Labeling was received from Guerbet in their submission of September 20, 2012. The 74 day letter was issued on December 3, 2013 and cited the following with regard to labeling: lack of a package insert for the vial and syringe presentations of the product and requested that Guerbet submit that labeling. Only the package insert for the pharmacy bulk package was submitted with the original application. A response to the 74 day letter was received later in December but Guerbet stated in the letter that during the Pre-NDA meeting the Division agreed that one label was sufficient for the product and therefore did not include the requested labeling in the December 31, 2012 submission.

The 74 day letter stated that the Division would provide a draft label to Guerbet on or near February 27, 2013 for their review and revision. Numerous revisions were made to the original label and the draft label from FDA was sent to Guerbet electronically on March 1, 2013. The Division requested a response by COB Wednesday, March 6, 2013. Guerbet expressed that the turnaround time was too short and requested that the deadline be extended to Friday, March 8, 2013. The Division agreed to this extension.

Review

The package insert from the September 20, 2012 submission was revised by the review team. Numerous changes were made to the package insert (see draft label of March 1, 2013-attached) and an information request containing the revised labeling was sent to Guerbet on March 1, 2013. Also included in the IR request to Guerbet were the following requested changes to the carton and immediate containers labels for the pharmacy bulk package, syringe, and vial.

March 1, 2013

Regarding the draft labeling for your pending NDA 204-781 for Dotarem, you should revise your labeling as requested and provide the following.

Immediate Container Labels and Immediate Container Cartons - single dose presentation

1. Revise the composition statement on the label for the immediate container for the vials, the cartons for the vials, the prefilled syringes and the prefilled syringe cartons for all fill sizes to match the composition statement in the revised package insert as follows:

    Each 1 mL contains: 376.9 mg of gadoterate meglumine, 0.25 mg DOTA and water for injection

PHARMACY BULK PACKAGE-PBP

2. The Immediate Container label for the 100 mL PBP vial and carton should state: "**NOT FOR DIRECT INFUSION**"

3. Revise the composition statement for the immediate container for the vials of the Pharmacy Bulk Package, and the cartons for the vials to match the composition statement in the revised package insert as follows:

    Each 1 mL contains: 376.9 mg of gadoterate meglumine, 0.25 mg DOTA and water for injection

4. Provide a separate revised package insert for the single dose presentations and the pharmacy bulk package of Dotarem.

FDA received the revised package inserts for the pharmacy bulk package and the syringe/vial on March 8, 2013. Those package inserts were reviewed and additional changes were made to the package inserts by FDA. A revised package insert for the vial/syringe was sent to Geuerbet on March 15, 2013 plus recommendations from DMEPA on the container/carton labels and the pharmacy bulk package. Guerbet was instructed to send revised package inserts for the vial/syringe and the pharmacy bulk package presentation. Guerbet revised the labels; accepted

most of the changes requested by FDA and returned the label to FDA on Monday March 18, 2013. The only changes made by Guerbet to the package insert were the following: in section 2.2 (PBP) (1) "The Pharmacy Bulk Package is not for use in direct intravenous infusion", (2)"The Pharmacy bulk Package is used as a multiple dose container with an appropriate transfer device for filling empty sterile syringes." Guerbet replaced the word "immediately" with the word "promptly" in the section 2.2 of the pharmacy bulk package label. Guerbet replaced the word "dysfunction" with the word "impairment" in section 5.3 of the of the vial/syringe label. As requested by FDA section 8.7 of the syringe/vial label was deleted. The changes made by Guerbet to the package insert were acceptable to FDA.

The carton and container labels were also reviewed. An artifact was noted on the immediate container label of the pharmacy bulk package and Guerbet was requested to change the label. Guerbet agreed to do so and submitted another label to FDA. The label was acceptable.

Recommendations

Based on Guerbet's acceptance of the changes to the package insert/container/carton labels, I recommend that FDA issue an approval letter for the Dotarem application.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

Supervisory Concurrence
Kyong Kang, PharmD.
Chief, Project Management Staff
March 20, 2013

PROJECT MANAGER LABELING REVIEW

14 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES W MOORE
03/20/2013

KYONG A KANG
03/20/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: 2021-2 A study that will examine patients 0-23 months of age who are referred for a contrast-enhanced MRI exam of the central nervous system. A sufficient number of subjects will be studied to adequately characterize the pharmacokinetics of the product in this age group. At least 40 subjects will be evaluated in this study and the study must include a sufficient number of subjects to adequately support the safety and efficacy of Dotarem for central nervous system MRI

PMR/PMC Schedule Milestones:		
	Draft Protocol Submission:	August, 2012
	Final Protocol Submission:	October, 2013
	Study/Trial Completion:	June, 2015
	Final Report Submission:	June, 2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☒ Small subpopulation affected
x Theoretical concern
☐ Other

Safety and efficacy of Dotarem was demonstrated in adults and children over two years of age. There is a theoretical concern about the Nephrogenic Systemic Fibrosis (NSF) risk in children less than two years of age due their immature renal function and possible prolonged gadolinium retention. This PMR is needed to assess safety and efficacy in this age group and to collect PK data . NDA contained no PK studies in children of any age.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

To evaluate pharmacokinetics and safety of Dotarem in children ages 0-23 months. Proposed study risk is renal immaturity.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☒ Assess a known serious risk related to the use of the drug?
     ☒ Assess signals of serious risk related to the use of the drug?
     ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open-label study in pediatric subjects (term newborn to 23 months) referred for an MRI with contrast for routine diagnostic purposes. Subjects must be clinically stable, have no contra-indications to MRI exam, and have no evidence of renal insufficiency, (eGFR < 80% of age-adjusted normal value calculated based on the Schwartz formula.)

Study initiation: Study to proceed after completion of a limited repeat dose administration (pre-clinical) study.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FINAL CLINICAL INSPECTION SUMMARY

DATE: March 19, 2013

TO: James Moore, Regulatory Project Manager
Barbara Stinson, D.O., Clinical Reviewer
Division of Medical Imaging Products

FROM John Lee, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D., Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D., Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 204-781

APPLICANT: Guerbet, LLC

DRUG: Dotarem® (gadoterate meglumine) Injection

NME: Yes

INDICATION: Enhancement of magnetic resonance imaging of the central nervous system in adult and pediatric patients to visualize disrupted blood brain barrier or abnormal vascularity

REVIEW CLASSIFICATION:	Priority
CONSULTATION REQUEST DATE:	November 20, 2012
INSPECTION SUMMARY GOAL DATE:	January 24, 2013
INTERIM SUMMARY REPORT DATE:	January 25, 2013
PDUFA DUE DATE:	March 20, 2013

Note to DMIP

An interim clinical inspection summary (CIS) was forwarded to DMIP (in DARRTS) on January 25, 2013. At that time, the inspection of Site 0702 in Study DGD-44-050 (Boys) had not been completed, and for the three completed inspections, the establishment inspection reports (EIRs) were not received from the field office (final outcomes pending). This final CIS includes preliminary results for Site 0702 in Study DGD-44-050 (Boys) and replaces preliminary results with final outcomes for two inspections (Guerbet and (b) (4)). This final CIS supersedes the previous interim CIS. For the two inspections without final outcomes shown in this final CIS (preliminary results only, Sites 702 and 719 in Study DGD-44-050), an addendum to this summary will be forwarded to DMIP if outcome classification changes or if additional observations of clinical or regulatory significance are discovered upon receipt and review of the EIRs.

I. Background

Contrast-enhanced magnetic resonance imaging (**MRI**) is considered the current "gold standard" for the non-invasive evaluation of central nervous system (**CNS**) pathology, including tumor, infection, inflammation, trauma, and demyelinating or degenerative disorders. Contrast enhancement of CNS lesions relies on disrupted blood-brain barrier (**BBB**) that permits the contrast agent to diffuse into lesions. Gadolinium, a rare earth element and a paramagnetic metal, is commonly used to produce contrast enhancement. There are seven gadolinium-based contrast agents (**GBCA**) on the market worldwide for use in CNS MRI, all with similar indications for use: Dotarem®, Magnevist®, ProHance®, Omniscan®, Gadovist®, Optimark®, and Multihance®. These GBCAs contain a gadolinium ion linked to different complexing agents with different chemical properties, including relaxivity relevant to image enhancement.

Dotarem® was first approved in 1989 in France as a contrast agent for use in intracranial and spinal MRI in adults, and subsequently in 70 countries worldwide for magnetic resonance angiography, whole body MRI, and for use in children. The Dotarem® clinical development program consists of 49 completed studies and 2813 patients. The CNS MRI indication is supported by 23 studies including three pivotal studies conducted under the United States (**US**) IND 65041: Studies DGD-03-44-A, DGD-44-051, and DGD-44-050. Study DGD-44-051 was a retrospective re-read study of the earlier negative Study DGD-03-44-A. In the current NDA, based on the two positive Studies DGD-44-051 and DGD-44-050, the sponsor seeks US marketing approval of Dotarem® for use in adult and pediatric MRI for the evaluation of CNS lesions with disrupted BBB or abnormal vascularity. To support priority review, the sponsor cites favorable benefit-risk in young children (age under two years) and in severe renal impairment.

Study DGD-03-44-A

Evaluation of MRI with Dotarem® in the diagnosis or follow-up assessment of cerebral or spinal tumors

This study was conducted at nine sites in Europe over 14 months, from August 2003 to October 2004. The primary objective was to confirm the efficacy of Dotarem® enhanced-MRI relative to non-enhanced MRI in characterizing CNS tumors, using tissue histopathology as the truth standard. Under a pair-controlled, intra-subject study design, 151 adult subjects with CNS tumors were evaluated using MRI before and after Dotarem® injection. Unenhanced and enhanced MRI images were obtained before and after the administration of Dotarem® as a single intravenous bolus (0.2 mL/kg). The images were interpreted by two blinded, independent off-site readers.

Subject Selection

- Inclusion criteria
  - Men or women (age $\geq$ 18 years) with known or suspected CNS (cerebral or spinal) neoplasm as evaluated by a previous CT or MRI
  - Scheduled for a contrast enhanced MRI examination and either a biopsy or surgery. Subjects should not present with non-tumoral cerebral disease.

- Female subjects should take effective contraception or should be surgically sterilized or have post-menopausal amenorrhea (for at least 12 months)

- Exclusion criteria
  - Non-neoplastic cerebral disease (e.g., inflammatory disease, multiple sclerosis, Alzheimer disease)
  - Contraindication to MRI (e.g., pacemaker, claustrophobia); allergy to gadolinium chelates

Endpoint Assessment

- Primary endpoint and analysis: Increased diagnostic accuracy, defined as proportion of subjects with additional lesions detected only on post-enhancement MRI (blinded readings, inter-reader concordance)
- Secondary endpoints and analyses: Comparison of off-site and on-site assessments
  - Sensitivity and specificity; positive and negative predictive values
  - Lesion number, location, size, and shape; lesion signal intensity, image quality, and artifacts
  - Delineation of lesion conspicuity (edema, necrosis, hemorrhage, calcification, cysts)
  - Changes in therapeutic management of the subjects
- Subject populations
  - Intent-to-treat (ITT): all enrolled subjects
  - Evaluable: available truth standard and both MRIs before and after Dotarem® injection
  - Per-protocol: evaluable without major protocol violations
  - Safety: any amount of study medication administered
- Clinical safety: AEs, injection site tolerance, vital signs, ECG findings, and laboratory results over at least 24 hours and at 48 and 72 hours (when feasible) after contrast agent administration

Major Findings

The accuracy of Dotarem® MRI, the primary efficacy assessment, was statistically not different from that of unenhanced MRI, and the statistically non-significant results favored unenhanced MRI: higher diagnostic accuracy and sensitivity (one of two readers), and higher specificity (both readers). Major secondary efficacy assessments, however, were statistically significant and supported Dotarem® efficacy:

- Image quality improved with Dotarem® use: proportions of well-defined lesions increased from 13% and 18% to 58% and 61% (respectively) for off-site readings, and from 26% to 71% for on-site reading. On-site diagnostic confidence increased from 38% to 77% (statistically significant) and changed the clinical management for nearly one-half of the subjects (69 of 151, 46%).
- 15 AEs in 11 subjects: 11 events (9 serious) were consistent with the underlying conditions and four minor events were considered plausibly related to Dotarem® (no new safety concerns).

The sponsor attributes the negative primary study findings to the unbalanced ratio of malignant versus benign tumors (75% malignant, 25% benign), which resulted in unenhanced MRI accuracy to be higher than anticipated (50%) and the inability to show increased accuracy of Dotarem® MRI (70% anticipated). The positive study findings were evaluated more rigorously in a retrospective re-read study in which the major secondary efficacy assessment was re-defined as the primary assessment, as described below.

Study DGD-44-051

Evaluation of MRI with Dotarem® in the diagnosis or follow-up assessment of cerebral or spinal tumors, Re-reading of MRI images

This was a retrospective study in which the original images from Study DGD-03-044-A were re-read by three central, independent, blinded radiologists (different readers from those in the original study). The re-read study was managed by a central imaging laboratory over five months, from September 2010 to February 2011. The evaluable and per-protocol populations contained 149 and 124 subjects, respectively.

Endpoint Assessment

- Co-primary endpoints and analyses: Difference in morphology score between two MRI modalities, unenhanced MRI alone versus paired MRI (unenhanced and enhanced read together), for each of three pre-defined morphology elements of lesion visualization.
  - The three pre-defined morphology elements consisted of border delineation, internal morphology, and degree of contrast enhancement.
  - For each subject, up to five largest lesions were selected. For each lesion, the three morphology elements were scored using a three-point scale: unevaluable 0, inadequate 1, and adequate 2.
  - For each morphology element, a subject score was calculated as the sum of all lesion scores. The difference in subject score between unenhanced and paired MRI served as a co-primary endpoint.
  - Dotarem® was to be considered effective if supported by a statistically significant difference in subject score for all three morphology elements in at least two of the three off-site blinded readers.
- Secondary endpoints and analyses: Comparisons at the subject level
  - Unenhanced MRI versus enhanced MRI: lesion visualization subject scores, diagnostic confidence, image quality, and increased signal intensity and signal-to-noise ratio
  - Unenhanced MRI versus paired or enhanced MRI: lesion visualization, intra-reader and inter-reader agreement in lesion visualization, change in lesion count, and impact on subject management

Major Findings

For all three readers, paired and enhanced MRI were statistically superior to unenhanced MRI alone in lesion visualization for all three morphology elements. Further:

- Two of three readers found paired images to be of significantly higher quality than unenhanced images.
- Higher image quality increased diagnostic confidence.
- Intra-reader and inter-reader agreement was higher for paired images than for unenhanced images.
- No significant difference was observed for lesion counts and clinical management.

To confirm the positive study findings, a new prospective study was conducted. The overall study design was similar to that of the original Study DGD-03-44-A but with study objectives and endpoints of the re-read Study DGD-44-051. The new study included pediatric subjects and the use of a currently approved MRI contrast agent as internal validation, as further described below.

Study DGD-44-050

Safety and efficacy evaluation of Dotarem® in magnetic resonance imaging (MRI) in patients with central nervous system (CNS) lesions (SENTIO Study)

The primary study objective was to demonstrate that MRI enhancement using Dotarem® is superior to unenhanced MRI in visualizing CNS lesions with disrupted BBB and/or abnormal vascularity (lesion border and internal morphology). This three-arm study was conducted over 14 months (September 2010 to November 2011) at 46 sites: 15 in US; six each in France and Germany; three each in Argentina, Austria, Chile, and Spain; two each in Brazil, Italy, and Korea; and one in United Kingdom. 402 subjects were enrolled: 364 adults randomized into two blinded groups, either Dotarem® (245 adults) or Magnevist® (119 adults), and 38 children enrolled (not randomized) into the third open-label group (Dotarem® only). Subjects served as their own control for both contrast agents; the study was powered to support the use of Magnevist® for internal validation (not as active control). Both contrast agents were given intravenously (0.2 mL/kg bolus). Within 28 days of screening, unenhanced MRI was followed immediately by enhanced MRI using either contrast agent. Images were read by three off-site (independent) and one on-site reader. All three arms were single-blinded for MRI interpretation (unenhanced versus enhanced), and the two adult arms were double-blinded for contrast agent identity.

Subject Selection

- Inclusion criteria
  - Adult and pediatric subjects (age ≥ two years) scheduled for enhanced MRI of the CNS
  - At least one known or suspected CNS lesion with disrupted BBB and/or abnormal vascularity
  - Women of child-bearing potential: effective contraception, surgically sterile, or post-menopausal
- Exclusion criteria
  - Acute or chronic renal insufficiency (Grade IV or V, glomerular filtration rate < 30 mL/min/1.73 m²)
  - Receipt of contrast agent within three days or anticipated receipt within 24 hours
  - Contraindication to MRI or known allergy to gadolinium chelates

Endpoint Assessment

- Co-primary endpoints and analyses in adult subjects: Difference in morphology score between two MRI modalities, unenhanced MIR alone versus paired MRI (unenhanced and enhanced read together), for each of three pre-defined morphology elements of lesion visualization.
  - The three pre-defined morphology elements consisted of border delineation, internal morphology, and degree of contrast enhancement.
  - For each subject, up to five largest lesions were selected. For each lesion, the three morphology elements were scored using a three-point scale: unevaluable 0, inadequate 1, and adequate 2.
  - For each morphology element, a subject score was calculated as the sum of all lesion scores. The difference in subject score between unenhanced and paired MRI served as a co-primary endpoint.
  - Dotarem® was to be considered effective if supported by a statistically significant difference in subject score for all three morphology elements in at least two of the three off-site blinded readers.
- Secondary endpoints and analyses: Adult primary endpoints and analyses applied to pediatric subjects (Dotarem® only), and the following new evaluations (comparisons at subject and lesion levels):
  - Comparison of unenhanced versus enhanced/paired MRI: lesion visualization, diagnostic confidence, image quality, signal intensity, intra-reader and inter-reader agreement, and lesion count
  - Comparison of contrast agents (Dotarem® versus Magnevist®): lesion visualization, lesion number and location, image quality, diagnostic confidence, and signal intensity
- Subject Populations
  - Intent-to-treat (ITT): all enrolled subjects
  - Evaluable: valid primary co-endpoint assessments
  - Per-protocol: evaluable without major protocol violations
  - Safety: injection of either contrast agent
- Clinical safety: AEs, injection site tolerance, vital signs, ECG findings, and laboratory results as evaluated at 24 ± 4 hours after contrast agent administration

Major Findings

- For all readers, lesion visualization (co-primary endpoints), image quality, signal-to-noise ratio, and diagnostic confidence were superior with paired or enhanced MRI than with unenhanced MRI. Read-results were not highly reproducible (moderate intra-reader and poor inter-reader agreement).
- Efficacy and safety results were not appreciably different between the two contrast agents (Dotarem® or Magnevist®), and efficacy results were consistent between adults (statistically significant) and children (statistically non-significant).

II. INSPECTION RESULTS

The inspection outcomes are shown in the table below. For this new molecular entity (**NME**) NDA, the pivotal Studies DGD-44-050 and DGD-44-051 were audited at good clinical practice (**GCP**) inspections of: (1) the sponsor (Guerbet, LLC), (2) the imaging contract research organization (**CRO**) (b) (4) and (3) two clinical study sites in Study DGD-44-050 (Boys, Site 0702; Burrowes, Site 0719).

The two clinical study sites in Study DGD-44-050 were selected based on: (1) being a pediatric site (Site 0719 only), (2) no prior FDA inspection history (both sites), and (3) large numbers of reported AEs and protocol violations relative to the numbers of subjects enrolled (both sites):

- Site 0702: 0.93 AEs and 1.3 protocol violations per (adult) subject reported in the NDA, with 16 of 22 (73%) of protocol violations for one Subject 070215 (40 year old woman) and only one of 16 total AEs at this site (6%) seen in the same Subject 070215 (mild hyperkalemia, uneventful resolution, and thought to be unrelated to the study medication)
- Site 0719: 1.0 AEs and 1.3 protocol violations per (pediatric) subject reported in the NDA, no notable occurrence pattern for AEs or protocol violations.

	Inspected Entity	Studies, Sites, & Subjects	Inspection Dates & Outcome
1	Guerbet, LLC 1185 West 2nd Street Bloomington, IN 47403	DGD-44-050, DGD-44-050, & DGD-03-44-A all sites & subjects	Jan 7 - 14, 2013 NAI
2	(b) (4)		
3	Gregory Boys, MD Clinical Trials of Texas, Inc. 7940 Floyd Curl Drive, Suite 700 San Antonio, Texas 78229	DGD-44-050, Site 0702 18 adult subjects	Jan 29 - Feb 6, 2013 final outcome pending (preliminary NAI)
4	Delilah Burrowes, MD Children's Memorial Hospital 2300 Children's Plaza, Mailbox 9 Chicago, Illinois 60614	DGD-44-050, Site 0719 7 pediatric subjects	Dec 31, 2012 - Jan 4, 2013 final outcome pending (preliminary NAI)

NAI = no action indicated (no significant deviations from regulations observed); VAI = voluntary action indicated (significant deviations from regulations observed); OAI = official action indicated (significant deviations from regulations and/or data unreliable warrant official regulatory action)

Pending: This preliminary outcome classification is based on information on Form FDA 483 and communication with the field investigator; final establishment inspection report has not been received from the field office and OSI's complete review of the report remains pending as of this clinical inspection summary.

Guerbet, LLC (Sponsor)

a. What was inspected:

- Applicable GCP regulations, to include adequacy of the sponsor's: (1) standard operating procedures (**SOPs**) for AE reporting and selecting (and monitoring) clinical study sites and CROs (and adherence to the SOPs); and (2) data management, including robustness of electronic controls over database interface, compatibility, and audit
- Test article handling and accountability, primary CRO contracts, Forms FDA 1572, and financial disclosure records

b. General observations:

- Form FDA 483 was not issued. The sponsor's records indicated adequate control over the various aspects of the audited studies. There was no evidence of image unblinding or biased image interpretation. No discrepancies or underreporting of protocol violations were observed. Drug accountability records were adequate.
- Three minor observations were verbally discussed and not cited on Form FDA 483 as they were not necessarily regulatory violations: (1) not alerting the FDA of discontinuing subject enrollment at a clinical study site, (2) not notifying the FDA of transferring regulatory obligations from the sponsor to a contract research organization, and (3) not assuring that each Form FDA 1572 was fully completed, to include documentation of the study site location.

  The most significant of these three verbal discussion items appears to be Item 1, the sponsor not electively notifying the FDA that a non-compliant study site (Site 0802, Study DGD-44-050) was prohibited from further subject enrollment (after enrolling 6 subjects) upon discovery of significant GCP non-compliance at a routine sponsor monitoring visit. The affected efficacy data were appropriately reported in the NDA as not having been collected per study protocol. The site was not terminated so that pending safety visits for the 6 subjects already enrolled (and given the study medication) could be completed. These discussion items (including Item 1) do not appear sufficiently important to require additional follow up regulatory investigation.

c. Assessment of data integrity: The data reported in the NDA appear reliable.

(b) (4)

Gregory Boys, M.D. (Study DGD-44-050, Site 0702)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects: 18 subjects were screened, 18 enrolled, and 16 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations:

- No significant deficiencies were observed and a Form FDA 483 was not issued.
  - IRB oversight and study monitoring appeared to be adequate. Informed assent was appropriately obtained for each subject according to applicable regulations.
  - Adherence to the study protocol was adequate, including subject eligibility determination, test article disposition and accountability, subject randomization, and the study blind.
  - Source records were well organized, complete, and matched corresponding CRFs.
- Verbal discussion (not cited on Form FDA 483):
  - Two ECGs (two subjects) were not performed within the protocol-specified timeframe due to equipment failure.
  - Urobilinogen was not included as part of the urinalysis for some subjects due to a procedural change at the testing laboratory.

c. Assessment of data integrity: Data from this study site appear reliable.

Note: Observations noted above for this Site 0719 of Study DGD-44-050 are based on preliminary communications with the field investigator.

Delilah Burrowes, M.D. (Study DGD-44-050, Site 0719)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects: 29 subjects were screened, 7 enrolled, and 7 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations:

This study site was an open-label single-arm pediatric site; all subjects at this site were pediatric subjects (age 3-16 years) given open-label Dotarem® (not randomized and blinded between Dotarem® and Magnevist® arms).

- No significant deficiencies were observed and a Form FDA 483 was not issued.
  - IRB oversight and study monitoring appeared to be adequate. Source records were neat, well organized, complete, and matched corresponding CRFs. Informed assent was appropriately obtained for each subject according to applicable regulations.
  - Adherence to the study protocol was adequate, including subject eligibility determination, test article disposition and accountability, subject randomization, and the study blind. Protocol violations that were reported to the sponsor (and subsequently reported by the sponsor in the NDA as protocol violations) were not cited on Form FDA 483.
- Verbal discussion (not cited on Form FDA 483): For one of two shipments of the study medication, the temperature range during shipment was not recorded.

Reviewer's Comments:

In general, the study results at this site support Dotarem® efficacy, safety, and intact Dotarem® product quality. However:

- *In one Subject 071907, the image quality did not improve with Dotarem® use; it is unclear if imaging could have improved also for this subject with more rigorous attention to product handling, including documentation of temperature control during shipment.*
- *The numbers of AEs and protocol violations were higher than expected relative to the number of subjects at this site. Not documenting the temperature range during shipment may be considered an unreported protocol violation, which may or may not have contributed subtly to an increase in AE rate and/or decreased product efficacy.*

Given the general context (inspection and site-specific NDA data), the observed deficiency nonetheless appears unlikely to have importantly impacted the study data or subject safety. If the data were impacted, Dotarem® would be more effective and safer than is supported by the actual data, and therefore the data from this site may be considered reliable.

c. Assessment of data integrity: Data from this study site appear reliable.

Note: Observations noted above for this Site 0719 of Study DGD-44-050 are based on preliminary communications with the field investigator.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

The conduct of three pivotal Dotarem® studies (described above, *Background*) was inspected for GCP compliance at four sites: sponsor (Guerbet), imaging CRO (b) (4) and two clinical study sites in Study DGD-44-050 (Site 0702, Boys; Site 0719, Burrowes).

At all four inspections, no significant deficiencies were observed and a Form FDA 483 was not issued. The studies appeared to have been conducted in accordance with the study protocol, established SOPs, and applicable GCP regulations. The efficacy data reported in the NDA were verifiable against the corresponding CRFs and source records. The data reported by the sponsor in the NDA appear reliable as evaluated at all four inspections.

The numbers of AEs and protocol violations reported at the two clinical study sites were higher than expected from the relatively small number of subjects. The reasons for the AE and protocol violation rates are unclear; the inspectional findings indicate due diligence in study conduct, including monitoring and reporting of AEs and protocol violations.

Note: For the two clinical site inspections, the EIRs have not been received from the field office and the final inspection outcomes remain pending. The observations noted above are based on preliminary communications with the field investigators. An addendum to this final CIS will be forwarded to DMIP if the outcome classification changes or if additional observations of clinical or regulatory significance are discovered upon receipt and review of the EIRs.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JONG HOON LEE
03/19/2013

SUSAN LEIBENHAUT
03/19/2013

SUSAN D THOMPSON
03/19/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: March 19, 2013

From: Erica Radden, M.D.
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader, Pediatrics Team
Pediatric and Maternal Health Staff, Office of New Drugs

Melissa S. Tassinari Ph.D., Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne P. Yao, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Dotarem (gadoterate meglumine)

Application Number: NDA 204-781; IND 65,041

Re: Input on pediatric development plan

Sponsor: Guerbet, LLC

Proposed Indication: For intravenous use with magnetic resonance imaging (MRI) in 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.

Dosage form and Route of administration: 376.9 mg gadoterate meglumine per mL (equivalent to 0.5 mmol/mL) in vial and pre-filled syringe administered intravenously.

Proposed Dosing regimen: Adults and children:
0.2 mL/kg (0.1 mmol/kg) body weight administered as an intravenous bolus injection at a flow rate of approximately 2 mL/second for adults and 1-2 mL/second for children delivered by manual of by power injection.

Consult Request:
"Please comment on the adequacy of the submitted data for patients under the age of 2. Specifically, for the three CNS studies conducted in ages 0 through 17 years, please comment on the adequacy of subject numbers (7 under age 2 years) and safety evaluations (most for AEs only) in the 0-23 months population clinical trial studies DGD 3-15 (laboratory parameters on 20/29 subjects with 2 subjects only under age 2 years), DGD-3-16 (AEs only), and DGD-3-29 (AEs only).

Please comment on the applicability of adult PK studies to pediatric population (no pediatric PK studies) and acceptability of dose (no dose ranging studies conducted in adults or peds).

Please comment on the proposed drug administration and labeling as it relates to the 3 pediatric studies. DGD-3-15 was carried out using study drug that was diluted in saline or that was not diluted and was administered at 3 mL/min. Study DGD3-16 used a flow rate of 2.4 ml/min. Study DGD-3-29 states a slow intravenous injection was used. None of these flow rates are reflected in the proposed labeling.

In addition, please review sections of the proposed label as they relate to pregnancy, lactation, pediatrics."

Materials Reviewed:
- NDA Orientation Meeting Package Slides (October 31, 2012)
- Proposed Dotarem labeling (October 30, 2012)
- Briefing documents for the Medical Imaging Drugs Advisory Committee (MIDAC) meeting held on February 14, 2013
- Gadavist (gadobutrol) approval letter (March 14, 2011)
- Gadavist (gadobutrol) approved labeling (March 14, 2011)
- Prior MHT review for Gadavist (gadobutrol) dated February 3, 2011
- Literature search of PubMed, Reprotox-MICROMEDEX and LactMed

Introduction:
On September 20, 2012, Guerbet, LLC submitted a new drug application (NDA 204-781) for Dotarem (gadoterate meglumine). Dotarem is a gadolinium-based contrast agent (GBCA) with a proposed indication for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonates to 17 years of age). The Division of Medical Imaging Products (DMIP) consulted the Pediatric and Maternal Health Staff (PMHS) to provide input on the sponsor's pediatric development plan, proposed drug administration and labeling related to pregnancy, lactation and pediatrics. In addition to product specific data, data reviewed previously regarding GBCA exposures during pregnancy has been incorporated into the labeling (See review on Gadavist by Leyla Sahin, MD, February 3, 2011).

Background:
Although gadoterate has been marketed in Europe since 1989 with an indication that includes pediatric patients of all ages, there are no GBCAs that are currently approved for use in children less than 2 years of age in the US. There is a boxed warning for the class of GBCAs due to the increased risk of Nephrogenic Systemic Fibrosis (NSF) among patients with impaired renal elimination such as those with chronic severe kidney disease (glomerular filtration rate [GFR] < 30 mL/min/1.73m^2) or acute kidney injury.

Reviewer comment: Healthy children do not attain a normal adult glomerular filtration rate until 1 year of age. Therefore, the boxed warning, though not explicitly stated, pertains to pediatric patients who have GFRs less than 30 mL/min/1.73m^2 as well.

A GBCAs molecular structure and physio-chemical stability confers varying propensities to liberate gadolinium which can lead to the interaction of "free" gadolinium with body organs and theoretically increase the risk of NSF. Macrocyclic agents, such as gadoterate dimeglumine, reportedly "cage" gadolinium and have the lowest propensity for the release of gadolinium. This product is the only ionic macrocylic GBCA which, the sponsor claims, may confer decreased risk of NSF due to greater thermodynamic and kinetic stability.

Reviewer comment: The sponsor has provided some data to support that claim. However, PMHS defers to DMIP to assess the validity of this assertion.

PMHS attended a Type C meeting November 13, 2012 in which an overview of the data included in the NDA application (dated September 20, 2012) was presented. PMHS also participated in several team meetings from December 3, 2012 to March 14, 2013, and a teleconference with the sponsor on February 20, 2013. PMHS also participated in preparation meetings for the Medical Imaging Drugs Advisory Committee (MIDAC) meeting held on February 14, 2013 and the Pediatric Review Committee (PeRC) meeting held on March 6, 2013.

Reviewer comment: The MIDAC voted 10 to 6 (with one member abstaining) not to recommend approval in pediatric patients less than 2 years of age. The committee

expressed concern with the paucity of data presented to support a novel indication for children under 2 years of age.

Pediatric Development Plan:
The sponsor submitted data from four clinical trials, 2496 pediatric patient exposures in six post-marketing surveillance studies and spontaneous pharmacovigilance reporting to support its application for approval in pediatric patients (neonates to age 17 years). Of the 137 pediatric patients enrolled in the single pivotal clinical safety and efficacy trial and the three open-label exploratory clinical trials, only seven patients were less than 2 years of age. However, the sponsor claims that there have been over 30 million exposures to Dotarem worldwide with approximately 52,000 in children less than 2 years of age between 2005 and 2012.

Several deficiencies have been identified by DMIP with the submitted data. The sponsor did not conduct pediatric pharmacokinetic or juvenile animal studies, and only two of the seven patients in the clinical trials had laboratory evaluations that included safety laboratory monitoring. Furthermore, the information from the post-marketing surveillance studies largely includes summary reports and no patient-level data or other details to allow further evaluation.

Reviewer comment: PMHS agrees with DMIP and the MIDAC that there are insufficient data to support an indication in patients less than 2 years of age. The number of patients less than 2 years of age included in the four submitted clinical trials (n=7) are not sufficient to establish efficacy in newborns and infants. Furthermore, there were no patients in the clinical trials less than 1 month of age. Extrapolation of efficacy may potentially be permissible from adequate and well controlled-studies in adults provided the pathophysiology of the disease is similar in adults and children and the effects of the drug are similar. DMIP has determined that efficacy is able to be extrapolated in children 2 years and older for GBCAs based on the approval for gadobutrol. However, the ability to extrapolate efficacy in patients less than 2 years of age is unclear. Additionally, pediatric dosing and safety data cannot be extrapolated. The small number of patients less than 2 years of age that were included in the clinical trials coupled with the limited follow-up and laboratory information obtained for patients in whom adverse events were reported is not adequate to establish the safety of Dotarem in patients less than 2 years of age. Finally, there are also no PK data on which to base dosing.

Comments on the Pediatric Research Equity Act (PREA):
Under PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Dotarem is a new molecular entity which constitutes a new ingredient, thereby prompting the requirement for pediatric studies.

The sponsor initially proposed that their submission fulfilled the pediatric assessment in all age groups, and therefore, did not submit a request for waiver or deferral of pediatric studies. However, given the concern that the sponsor's data for pediatric patients less than 2 years of age was inadequate to grant an indication in this subpopulation, the sponsor was advised to submit a request for deferral of studies in pediatric patients age 0 to 23 months. (b) (4)
The division is currently negotiating the pediatric study requirements with the sponsor. The PREA PMRs will likely be similar to those requested for Gadavist which are as follows:

> 1743-1 You must provide additional nonclinical (animal) data to support the safety of your product in the 0-23 month pediatric age group. These nonclinical data should be obtained from newborn to juvenile animals that model pediatric patients in this age group. The study will examine the safety of the product in newborn and neonatal animals, following a single dose and limited repeated dose administrations.
>
> 1743-2. Your study will examine patients 0-23 months of age who are referred for an MRI exam with contrast. A sufficient number of subjects will be studied to adequately characterize the pharmacokinetics of the product in this age group. At least 40 patients will be evaluated in this study, and the study must include a sufficient number of subjects to adequately support the efficacy of Gadavist for central nervous system MRI.[1]

Reviewer comment: PMHS defers to Pharmacology/Toxicology for details of design of the study, but agrees that juvenile animal studies could further elucidate the risk of NSF associated with the use of this product in children less than 2 years of age could inform the conduct of clinical trials in newborns and infants. Additionally, PMHS agrees with the need for a PK study, but defers to Clinical Pharmacology regarding the details of design. A lab evaluation of renal function to include urinalysis and creatinine levels should be included in the protocol of the PK study as well.

DMIP presented Dotarem at the PeRC meeting on March 6, 2013, and the PeRC agreed with the division's plan.

Comments on Dosing:
PMHS notes that the dosage for Gadavist was selected based on approved dosing for other GBCAs, and the flow rate for Dotarem administration differs in each of the submitted clinical trials. However, PMHS defers to Clinical Pharmacology to determine the appropriate dosing regimen for labeling.

Pregnancy and Nursing Mothers Labeling:
The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling.

[1] Gadavist (gadobutrol) approval letter (March 14, 2011)

This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the Pregnancy and Nursing Mothers labeling subsections. In addition, the MHT works with the pharmacology/toxicology reviewers to present animal data, in the Pregnancy and Nursing Mothers subsections, to make it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, animal dose including human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For the Nursing Mothers subsection, when animal data are available, only the presence or absence of drug in milk is presented in the label. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

Sponsor's Proposed Labeling:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

(b) (4)

(b) (4)

8.3 Nursing Mothers

(b) (4)

8.4 Pediatric Use

(b) (4)

Discussion on Labeling Recommendations:

Pregnancy and Nursing Mothers Labeling

PMHS-MHT conducted a review of literature and practice guidelines regarding pregnancy and lactation for Gadavist, another GBCA, and provided labeling recommendations related to pregnancy and lactation. (See review on Gadavist by Leyla Sahin, MD, February 3, 2011.) The approved Pregnancy and Nursing Mothers labeling for Gadavist was used as a model for these sections of the Dotarem labeling. A current literature review was conducted searching for human exposures of gadolinium contrast agents during pregnancy or lactation since the prior Gadavist review using PubMed, LactMed, and Reprotox-MICROMEDEX. The following terms were used to perform the PubMed search: pregnancy and gadolinium, pregnancy and gadoterate meglumine, lactation/breastfeeding and gadolinium, and lactation/breastfeeding and gadoterate meglumine.

Three additional studies regarding gadolinium exposure in pregnancy were found in a review of the open source literature. One study evaluating diagnosis of placenta acreta with MRI described 6 pregnant women at 34-38 gestational weeks who received gadopentetate dimeglumine (Magnevist). Although the births were notable for fetal distress with 2 neonates and meconium staining with another, none of the infants had any

sequelae at the time of discharge.[2] No adverse events to the fetus were noted in another study of 29 pregnant women with a mean gestational age of 27 weeks (ranging from 13–31 weeks) who underwent MRI for acute abdominal and pelvic pain in which seven women received a GBCA (0.1 mmol/kg gadodiamide [Omniscan]) to aid in the diagnosis.[3] Eleven women at 19–34 weeks of gestation were studied for symptomatic hydronephrosis in which they were injected with 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist) with no reported short-term adverse effects to the neonates.[4] Additionally, no long-term outcome studies or data were identified.

As noted in the Gadavist review, limited post-marketing data exist on the exposure of pregnant or lactating women to gadolinium agents. No studies were found reporting data after exposure in pregnancy to Dotarem. Therefore, the long term-risks to children exposed to Dotarem in utero are unknown. However, the limited available human data on gadolinium agents used during pregnancy or lactation should be included in labeling. Although use of gadolinium products is not recommended in pregnancy, there may be situations when the potential benefit to the mother and/or fetus may outweigh the risk.

There appears to be a low risk of exposure to GBCAs in breastfeeding infants because there is minimal excretion of GBCAs in breast milk, and nonclinical and human study data suggest that limited systemic absorption occurs with oral administration of gadolinium-DTPA.[5]

Pediatric Use Labeling

Since gadoderate will likely be approved only in pediatric patients 2 years and older, information regarding pediatric use should be placed throughout labeling for the approved pediatric age groups. PMHS-pediatric team recommends that (b) (4) be replaced with "pediatric patients" throughout labeling and the age of indication be changed from (b) (4) or (b) (4) to "patients 2 years and older". A weight based dosing table is included in the Dosing and Administration section. Because dosage adjustments based on weight are recommended, the statement that (b) (4) should be qualified by stating "no dosage adjustment based on age is necessary". Also, because an indication is unlikely to be granted in pediatric patients less than 2 years of age, the lack of established safety and efficacy in this subpopulation should be noted. Given the boxed warning regarding the potential for NSF in patients with impaired renal function (GFR < 30 mL/min/1.73m^2), a population that includes pediatric patients with immature kidneys,

[2] Tanaka Yo, Sohda S, Shigemitsu S, Niitsu M, Itai Y. High temporal resolution dynamic MRI in a high risk group for placenta accreta. *Magn Reson Imaging* 2001; **19**: 635–642.
[3] Birchard KR, Broan MA, Hyslop WB, Firat Z, Semelka RC. MRI of acute abdominal and pelvic pain in pregnant patients. *AJR Am J Roentgenol.* 2005; **184**: 452–458.
[4] Spencer JA, Tomlinson AJ, Weston MJ, Lloyd SN. Early report: comparison of breath-hold MR excretory urography, Doppler ultrasound and isotope renography in evaluation of symptomatic hydronephrosis in pregnancy. *Clin Radiol* 2000; **55**: 446–453.
[5] Laniado M, et al. MR imaging of the gastrointestinal tract: value of Gd-DTPA. *Am J Roentgenology* 1988:150; 817-821

PMHS recommends adding that GFR does not reach adult levels until 1 year of to specifically alert clinicians about this potential risk in the pediatric population.

PMHS Recommended Labeling:

Provided below are PMHS' recommended revisions to the sponsor's proposed labeling based on labeling from September 20, 2012 and last edited on March 15, 2013. This version of the labeling includes recommendations made by the Toxicology Reviewers, Dr. Olayinka Dina and Adebayo Laniyonu.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with DOTAREM Injection conducted in pregnant women. Limited published human data on exposure to other GBCAs during pregnancy did not show adverse effects in exposed neonates. No effects on embryo-fetal development were observed in rats or rabbits at doses up to 10 mmol/kg/day in rats or 3 mmol/kg/day in rabbits. The doses in rats and rabbits were 16 and 10 times, respectively, the recommended human dose based on body surface area. DOTAREM Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

While it is unknown if DOTAREM Injection crosses the human placenta, other GBCAs cross the placenta in humans and result in fetal exposure.

Animal Data

Reproductive and developmental toxicity studies were conducted with gadoterate meglumine in rats and rabbits. Gadoterate meglumine was administered intravenously in doses of 0, 2, 4 and 10 mmol/kg/day (or 3.2, 6.5 and 16.2 times the recommended human dose based on body surface area) to female rats for 14 days before mating through gestation day (GD) 17. Pregnant rabbits were intravenously administered gadoterate meglumine at the dose levels of 0, 1, 3 and 7 mmol/kg/day (3.3, 10 and 23 times the human doses based on body surface area) from GD6 to GD19. No effects on embryo-fetal development were observed in rats or rabbits at doses up to 10 mmol/kg/day in rats or 3 mmol/kg/day in rabbits. Maternal toxicity was observed in rats at 10 mmol/kg/day (16 times the human dose based on body surface area) and in rabbits at 7 mmol/kg/day (23 times the human dose based on body surface area).

8.3 Nursing Mothers

It is not known whether DOTAREM Injection is excreted in human milk. Limited case reports on the use of GBCAs in nursing mothers indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in breast milk. Because many drugs are excreted in human milk, exercise caution when DOTAREM Injection is administered to a nursing woman. Data from animal studies show that absorption via the gastrointestinal tract is poor and gadoterate meglumine is excreted into milk in very small amounts (<0.1% of the dose intravenously administered).

8.4 Pediatric Use

The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg have been established in pediatric patients from 2 to 17 years of age. No dosage adjustment according to age is necessary in this population *[See Dosage and Administration (2.1) and Clinical Studies (14)]*. The safety and efficacy of DOTAREM have not been established in pediatric patients below 2 years of age. GFR does not reach adult levels until one year of age *[see Warnings and Precautions (5.1)]*.

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/s/

ERICA D RADDEN
03/19/2013

HARI C SACHS
03/20/2013

MELISSA S TASSINARI
03/20/2013

LYNNE P YAO
03/20/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	March 14, 2013
Reviewer:	Kevin Wright, PharmD Division of Medication Error and Prevention and Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error and Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error and Prevention Analysis
Drug Name and Strengths:	Dotarem (Gadoterate Meglumine) Injection, 5 mmol per 10 mL (0.5 mmol per mL) 7.5 mmol per 15 mL (0.5 mmol per mL) 10 mmol per 20 mL (0.5 mmol per mL) 50 mmol per 100 mL (0.5 mmol per mL)
Application Type/Number:	NDA 204781
Applicant/Sponsor:	Guerbet, LLC
OSE RCM #:	2012-2837

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Dotarem under NDA 204781 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted NDA 204781 for Dotarem (Gadoterate meglumine) to the Agency on September 20, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the September 20, 2012 NDA submission.

- Active Ingredient: Gadoterate Meglumine
- Indication of Use: indicated for intravenous use with magnetic resonance imaging (MRI) in brain, spine, and associated tissues in adults and pediatric patients to detect and visualize areas with disruption of the blood brain barrier
- Route of Administration: Intravenous
- Dosage Form: Solution for Injection
- Strength: 0.5 mmol per mL (equivalent to 376.9 mg per mL)
- Dose and Frequency: 0.2 mL/kg (0.1 mmol/kg) as a bolus dose
- How Supplied:
    - Glass vials: 10 mL, 15 mL, 20 mL
    - Pre-filled syringe: 10 mL, 15 mL, 20 mL
    - Pharmacy bulk package: 100 mL vial
- Storage: Store at room temperature 25°C
- Container and Closure System:
    - Vials: type 1 glass vial with rubber stopper
    - Pre-filled syringe: type 1 glass syringe with gray tip caps

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS (FAERS) database for medication error reports related to gadolinium based contrast agents (GBCA) supplied in pre-filled syringes since Dotarem also proposes to use this container closure system. We also reviewed the Dotarem labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	January 28, 2013
Drug Names	Gadopentetate (active ingredient) Gadoteridol (active ingredient) Gadobutrol (active ingredient) Gadoversetamide (active ingredient)
MedDRA Search Strategy	Overdose (PT) Underdose (PT) Accidental Overdose (PT) Intercepted Drug Dispensing Error (PT) Drug Administration Error (PT) Incorrect Dose Administered (PT)

The FAERS and ISMP database searches identified 17 cases. Each case was reviewed for relevancy and duplication. After individual review, 11 cases were not included in the final analysis for the following reasons:

- Adverse events not related to medication error(s).
- Product Quality Issues.

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Vial Labels submitted on September 20, 2012(Appendix B through D)
- Vial Carton Labeling submitted on September 20, 2012 (Appendix E through G)
- Pre-filled Syringe labels submitted on September 20, 2012 (Appendix H through J)
- Pre-filled Syringe Carton labeling submitted on September 20, 2012 (Appendix K through M)
- Bulk Package label submitted on September 20, 2012 (Appendix N)
- Bulk Package Carton labeling submitted on September 20, 2012 (Appendix O)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Insert Labeling submitted September 20, 2012 (no image)

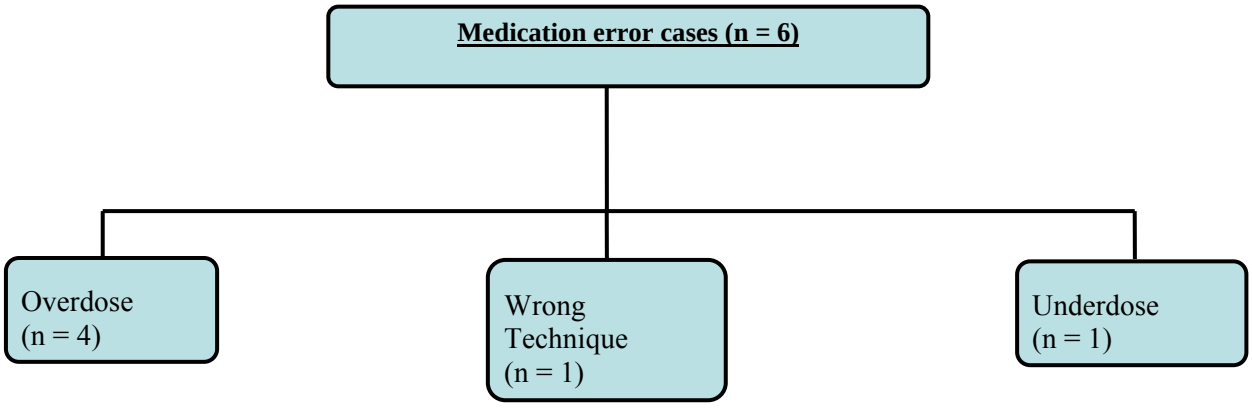
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Dotarem product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, six medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix H provides listings of all case numbers for the cases summarized in this review.

Figure 1: Medication errors related to Gadolinium Based Contrast Agents (n = 6) categorized by type of error



Overdose (n = 4)

Four cases (Case# 4193148 v2, Case# 6332299 v1, 6332791 v1, 6795206 v1) describe overdoses occurring with gadolinium based contrast agents. In one case (Case# 6795206 v 1) a patient was administered 20 mL instead of the prescribed dose of 12 mL. There was no other information provided in the other cases regarding the prescribed dose versus the administered dose. In three of the four cases (Case# 4193148 v2, Case# 6332299 v1, 6332791 v1) patients developed nephrogenic systemic fibrosis (NSF) as a result of the overdose.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

Wrong Technique (n = 1)

One case (Case# 7722148 v1) described a technologist attempting to stop an infusion once he/she noted infiltration during the procedure. The patient complained of pain at the injection, but recovered.

Underdose (n = 1)

One case (Case# 7237478 v1) described off label use of a gadolinium based contrast agent that resulted in sub-optimal images. The procedure was rescheduled. There were no outcomes reported for this event.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

The Applicant proposes multiple product presentations (i.e. vials, syringes, bulk package) for use by technologists and radiologists. As proposed, DMEPA has several safety concerns regarding the labeling and the design of this product.

DMEPA recommends the Applicant revise Table 1 in "Section 2 Dosage and Administration" to display the dose (i.e. mL) of Dotarem based on body weight (i.e. kg). (b) (4)

DMEPA recommends that the "directions for use" appearing in "Section 16 How Supplied" appear in "Section 2 Dosage and Administration". The *directions for use* instructing the end user on the proper technique on using the syringe pertains to the dosing and administering of the product and should appear in "Section 2.2 Drug Handling". DMEPA recognizes that the Division of Medical Imaging Products does not agree that this information should be placed in "Section Dosage and Administration" and maintains that the information will appear in "Section 16 How Supplied/Storage and Handling".

The Applicant proposes to introduce a pharmacy bulk package for Dotarem. The pharmacy bulk package is designed to prepare multiple doses from a single source within a designated period of time. DMEPA recognizes that the pharmacy bulk package is not unique to Dotarem. However, recent medication safety reports, have generated concern regarding the appropriateness of the product design and use of pharmacy bulk packages. Inappropriate use of a similar product presentation (i.e. single dose vials) has resulted in hospitalization of patients for bacterial infections[3]. The Applicant has provided microbiology data to support a product expiry of 24 hours in the manufacturer's container.

[2] http://www.ismp.org/pressroom/PR20110929.pdf, Last accessed 02/04/13.

[3] http://ismp.org/newsletters/acutecare/issue.asp?dt=20120920, Last accessed February 21, 2013.

The Applicant has not provided microbiology or stability data for Dotarem once the product is transferred to a delivery device. Without any microbiology or stability data then these syringes should be used immediately.

However, the pharmacy bulk package should be hung under an aseptic environment in a pharmacy to prepare the individual patient syringe. If the patient syringe is prepared in a pharmacy, then the syringe cannot be administered immediately because it will have to be transported to an imaging suite. Thus, we question if the pharmacy bulk package is an appropriate presentation for this product. Thus, on March 13, 2013 a meeting was held with representatives from DMIP, ONDQA, DMEPA and microbiology. Issues concerning the appropriate use and misuse of the bulk pharmacy packaging were discussed. The microbiology reviewer stated that the Applicant has submitted data demonstrating Dotarem has antimicrobial properties. Therefore, there appears to be little risk of the product developing microbial growth if the product is transferred into a syringe and not used (b) (4) as currently written in the proposed label. ONDQA acknowledged that no studies have been completed to indicate if the product promotes leachable substances from the syringe. However, the risk concerning leachable contamination also appears low, because the product should be administered (b) (4) The group discussed the use of the word (b) (4) in the proposed labeling. The group noted the product can not be transferred to a syringe and administered (b) (4) if the bulk package is hung under a hood in a pharmacy. The only way to administer the product (b) (4) would be to withdraw doses from the bulk package in an imaging suite, which is not the intended location of use. To help prevent healthcare providers from interpreting the word (b) (4) to mean the product should be only used in an imaging suite, the meeting representatives agreed the word immediately should be revised to the word "promptly".

The Applicant proposes (b) (4)

we recommend the Applicant revise the scale on the syringe label to conform with other syringe labels in this class of medication to mitigate confusion.

4 RECOMMENDATIONS

DMEPA provides the following comments for consideration by the review divison prior to the approval of this NDA:

I. Comments to the Division

DMEPA provides the following comments for consideration by the review divison prior to the approval of this NDA:

A. We recommend Table 1 be revised to only display the weight in kilograms, because the labeled dosing is based upon kilograms.

II. Comments to the Applicant

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Vial Label

1. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2. Revise the proprietary name on the vial label to title case (i.e. Dotarem) to improve the readability of the proprietary name.
3. Revise the statement of strength (e.g. 0.5 mmol/mL) to read total strength per total volume (e.g. 5 mmol per 10 mL) as the primary and most prominent expression throughout the labeling, followed in close proximity by strength per mL (e.g. 5 mmol per mL) enclosed in parentheses as recommended in accordance with the labeling standards found in the United States Pharmacopeia (USP) General Chapters <1> Injections.
4. Ensure the statement of strength follows in close proximity the established name. The proprietary name, established name, and statement of strength should be the most prominent information on the label. This information should be presented in the following format: proprietary name followed by established name followed by statement of strength.

Dotarem
(Gadoterate Meglumine) Injection
x mmol per/xx mL
(0.5 mmol/mL)

5. The dark blue text on the light blue background does not provide sufficient color contrast. Thus, to improve readability of the information printed on the vial label, revise the coloring scheme of the background or text to allow for greater contrast between the product information and the product packaging.
6. Revise the statement "STERILE SOLUTION" to appear in title case as "Sterile Solution".
7. Revise the statement "SINGLE USE VIAL" to appear in title case and the phrase Discard Unused Portion should appear immediately following or below the package type statement to appear as "Single Use Vial. Discard Unused Portion".
8. Revise the statement (b) (4) to read "each mL".

B. Carton Labeling

1. See comments A.1 through A.8 and revise the carton labeling accordingly.
2. Delete graphic appearing above the statement "For Intravenous Administration". The graphic of the vials does not convey any important information to the end user and the use of vials are common in this practice setting.

C. Syringe Label

1. See comments A.1 through A.4 and A.6 and revise the carton labeling accordingly.
2. Revise the statement "SINGLE USE SYRINGE" to appear in title case and the phrase Discard Unused Portion should appear immediately following or below the package type statement to appear as "Single Use Syringe, Discard Unused Portion".
3. Revise the scales on the 10 mL, 15 mL and 20 mL syringes to only show the volume contained or remaining in the syringe, and not the volume delivered or administered.

D. Syringe Carton Labeling

1. See comments A.1 through A.6, A8 and C.2and revise the carton labeling accordingly.
2. Delete graphic appearing above the statement "For Intravenous Administration". The graphic of the syringe does not convey any important information to the end user and the use of syringes are common in this practice setting.

E. Bulk Package Label

1. See comments A.1 through A.6 and revise the label accordingly.
2. Delete the graphic showing the bulk package hanging. The use of this graphic does not convey the context of use for this product.
3. Revise the entire text on the side panel that begins with "DOTAREM PHARMACY BULK…" to appear in title case to improve the readability of this information.
4. Add the statement "Withdraw Contents Within 24 Hours" to the principle display panel.
5. Consider incorporating transfer labels for patient specific doses on the bulk container. This will allow the end user to label patient specific doses immediately. The label should include the following information: Drug name, strength, and date and time. If space permits include area for a patient identifier (e.g. patient initials, patient#, etc.).

F. Bulk Package Carton Labeling

1. See comments A.1 through A.6, A8, E.2, E.3, and E.4 and revise the carton labeling accordingly.
2. Delete graphic appearing above the statement "For Intravenous Administration". The graphic of the vial does not convey any important information to the end user. The image does not convey that this package is a pharmacy bulk package.
3. Highlight the statement "Pharmacy Bulk Package Not for direct infusion".

G. Insert Labeling - Dosage and Administration Section

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.[4] As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the abbreviations, symbols, and dose designations as follows:
    - Revise all instances of trailing zeroes appearing in the text and tables of the Section 2 (Dosage and Administration). Trailing zeros are dangerous dose designations that could be misinterpreted as a 10 fold dose if the trailing zero is not seen (e.g., 1.0 mL as the final injection volume may be misinterpreted as 10 mL final injection volume).

If you have further questions or need clarifications, please contact Sandra Rimmel, project manager, at 301-796-2445.

[4] http://www.ismp.org/Tools/errorproneabbreviations.pdf, Last accessed 10/28/2009.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN WRIGHT
03/14/2013

SCOTT M DALLAS on behalf of YELENA L MASLOV
03/14/2013

SCOTT M DALLAS
03/14/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 2/20/2013

To: James W Moore, Regulatory Project Manager
Division of Medical Imaging Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Drug Promotion

Subject: Comments on draft labeling (Package Insert) for NDA 204781, Dotarem (gadoterate meglumine) Injection for Intravenous Use

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In response to your labeling consult request on November 29, 2012, we have reviewed the draft Package Insert for Dotarem and offer the following comments. Note that this review was based upon the February 19, 2013 version of the label.

Section	Statement	Comment
2.1 Dosing Guidelines	(b) (4)	(b) (4)
5.1 Nephrogenic Systemic Fibrosis	(b) (4)	(b) (4)

	(b) (4)	(b) (4)
5.2 Hypersensitivity Reactions	"Some patients experienced circulatory collapse and died."	The presentation of this section minimizes the risk of hypersensitivity with Dotarem by failing to give prominence to the most serious risk information. According to the statement, patients have died as a result of hypersensitivity to Dotarem. This information is included in 5.2 toward the end of the section in the middle of a paragraph. We recommend presenting the information in order of importance and present the potential of death first.
5.2 Hypersensitivity Reactions	"In most cases, initial symptoms occurred within minutes of Dotarem administration…"	This statement fails to include important contextual information. Most cases occurred within minutes, but what was the time to presentation of the more delayed events. This information is important for patient monitoring purposes to detect delayed reactions. Gadavist, for example states, "Delayed reactions can occur up to several days after administration." We recommend including information on delayed hypersensitivity reactions.
6.1 Clinical Studies Experience <u>Adverse Reactions in Children</u>	(b) (4)	(b) (4)
6.2 Post marketing Experience	(b) (4)	(b) (4)

	(b) (4)	(b) (4)
12.3 Pharmacokinetics	Table 4, Population column	We recommend including the creatinine clearance boundaries for each population listed in the chart. For example: Patients with moderate renal impairment (CrCl xx-xx mL/min)
14 Clinical Trials	(b) (4)	(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES S DVORSKY
02/20/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

INTERIM CLINICAL INSPECTION SUMMARY

DATE: January 24, 2013

TO: James Moore, Regulatory Project Manager
Barbara Stinson, D.O., Clinical Reviewer
Division of Medical Imaging Products

FROM John Lee, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D., Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D., Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 204-781

APPLICANT: Guerbet, LLC

DRUG: Dotarem® (gadoterate meglumine) Injection

NME: Yes

INDICATION: Enhancement of magnetic resonance imaging of the central nervous system in adult and pediatric patients to visualize disrupted blood brain barrier or abnormal vascularity

REVIEW CLASSIFICATION:	Priority
CONSULTATION REQUEST DATE:	November 20, 2012
INSPECTION SUMMARY GOAL DATE:	January 24, 2013
DMIP ACTION GOAL DATE:	March 13, 2013
PDUFA DUE DATE:	March 20, 2013

I. Background

Contrast-enhanced magnetic resonance imaging (**MRI**) is considered the current "gold standard" for the non-invasive evaluation of central nervous system (**CNS**) pathology, including tumor, infection, inflammation, trauma, and demyelinating or degenerative disorders. Contrast enhancement of CNS lesions relies on disrupted blood-brain barrier (**BBB**) that permits the contrast agent to diffuse into lesions. Gadolinium, a rare earth element and a paramagnetic metal, is commonly used to produce contrast enhancement. There are seven gadolinium-based contrast agents (**GBCA**) on the market worldwide for use in CNS MRI, all with similar indications for use: Dotarem®, Magnevist®, ProHance®, Omniscan®, Gadovist®, Optimark®, and Multihance®. As GBCAs, they all contain a gadolinium ion linked to a complexing agent but otherwise differ in chemical structure, stability, viscosity, pharmacokinetics, and relaxivity (image enhancement).

Dotarem® was first approved in 1989 in France as a contrast agent for use in intracranial and spinal MRI in adults, and subsequently in 70 countries worldwide for magnetic resonance angiography, whole body MRI, and for use in children. The Dotarem® clinical development program consists of 49 completed studies and 2813 patients. The CNS MRI indication is supported by 23 studies including three pivotal studies conducted under the United States (**US**) IND 65041: Studies DGD-03-44-A, DGD-44-051, and DGD-44-050. Study DGD-44-051 was a retrospective re-read study of the earlier negative Study DGD-03-44-A. In the current NDA, based on the two positive Studies DGD-44-051 and DGD-44-050, the sponsor seeks US marketing approval of Dotarem® for use in adult and pediatric MRI for the evaluation of CNS lesions with disrupted BBB or abnormal vascularity. To support priority review, the sponsor cites favorable benefit-risk in young children (age under two years) and in severe renal impairment.

Study DGD-03-44-A

Evaluation of MRI with Dotarem® in the diagnosis or follow-up assessment of cerebral or spinal tumors

This study was conducted at nine sites in Europe over 14 months, from August 2003 to October 2004. The primary objective was to confirm the efficacy of Dotarem® enhanced-MRI relative to non-enhanced MRI in characterizing CNS tumors, using tissue histopathology as the truth standard. Under a pair-controlled, intra-subject study design, 151 adult subjects with CNS tumors were evaluated using MRI before and after Dotarem® injection. Unenhanced and enhanced MRI images were obtained before and after the administration of Dotarem® as a single intravenous bolus (0.2 mL/kg). The images were interpreted by two blinded, independent off-site readers.

Subject Selection

- Inclusion criteria
  - Men or women (age $\geq$ 18 years) with known or suspected CNS (cerebral or spinal) neoplasm as evaluated by a previous CT or MRI
  - Scheduled for a contrast enhanced MRI examination and either a biopsy or surgery. Subjects should not present with non-tumoral cerebral disease.
  - Female subjects should take effective contraception or should be surgically sterilized or have post-menopausal amenorrhea (for at least 12 months)
- Exclusion criteria
  - Non-neoplastic cerebral disease (e.g., inflammatory disease, multiple sclerosis, Alzheimer disease)
  - Contraindication to MRI (e.g., pacemaker, claustrophobia); allergy to gadolinium chelates

Endpoint Assessment

- Primary endpoint and analysis: Increased diagnostic accuracy, defined as proportion of subjects with additional lesions detected only on post-enhancement MRI (blinded readings, inter-reader concordance)

- Secondary endpoints and analyses: Comparison of off-site and on-site assessments
  - Sensitivity and specificity; positive and negative predictive values
  - Assessment of lesion number, location, size, and shape
  - Assessment of lesion signal intensity, image quality, artifacts
  - Delineation of lesion conspicuity (edema, necrosis, hemorrhage, calcification, cysts)
  - Changes in therapeutic management of the subjects
- Subject populations
  - Intent-to-treat (ITT): all enrolled subjects
  - Evaluable: available truth standard and both MRIs before and after Dotarem® injection
  - Per-protocol: evaluable without major protocol violations
  - Safety: any amount of study medication administered
- Clinical safety: AEs, injection site tolerance, vital signs, ECG findings, and laboratory results as evaluated over at least 24 hours and at 48 and 72 hours (when feasible) after contrast agent administration

Major Findings

The accuracy of Dotarem® MRI, the primary efficacy assessment, was statistically not different from that of unenhanced MRI, and the statistically non-significant results favored unenhanced MRI: higher diagnostic accuracy and sensitivity (one of two readers), and higher specificity (both readers). Major secondary efficacy assessments, however, were statistically significant and supported Dotarem® efficacy:

- The image quality improved with Dotarem® use: the proportions of well-defined lesions increased from 13% and 18% to 58% and 61% (respectively) for the two off-site readings, and from 26% to 71% for the on-site reading.
- Similarly, on-site diagnostic confidence increased from 38% to 77% (statistically significant), and effected a change in therapeutic management for nearly one-half of the subjects (69 of 151, 46%).
- Of the 15 AEs reported for 11 subjects, 11 events (9 serious) were consistent with the underlying conditions and four minor events were considered plausibly related to Dotarem® (no new safety concerns identified).

The sponsor attributes the negative primary study findings to the unbalanced ratio of malignant versus benign tumors (75% malignant, 25% benign), which resulted in unenhanced MRI accuracy to be higher than anticipated (50%) and the inability to show increased accuracy of Dotarem® MRI (70% anticipated). The positive study findings were evaluated more rigorously in a retrospective re-read study in which the major secondary efficacy assessment was re-defined as the primary assessment, as described below.

Study DGD-44-051

Evaluation of MRI with Dotarem® in the diagnosis or follow-up assessment of cerebral or spinal tumors, Re-reading of MRI images

This was a retrospective study in which the original images from Study DGD-03-044-A were re-read by three central, independent, blinded radiologists (different readers from those in the original study). The re-read study was managed by a central imaging laboratory over five months, from September 2010 to February 2011. The evaluable and per-protocol populations contained 149 and 124 subjects, respectively.

Endpoint Assessment

- Co-primary endpoints and analyses: Difference in morphology score between two MRI modalities, unenhanced MRI alone versus paired MRI (unenhanced and enhanced read together), for each of three pre-defined morphology elements of lesion visualization.

- The three pre-defined morphology elements consisted of border delineation, internal morphology, and degree of contrast enhancement.
- For each subject, up to five largest lesions were selected. For each lesion, the three morphology elements were scored using a three-point scale: unevaluable 0, inadequate 1, and adequate 2.
- For each morphology element, a subject score was calculated as the sum of all lesion scores. The difference in subject score between unenhanced and paired MRI served as a co-primary endpoint.
- Dotarem® was to be considered effective if supported by a statistically significant difference in subject score for all three morphology elements in at least two of the three off-site blinded readers.

- Secondary endpoints and analyses: Comparisons at the subject level
  - Unenhanced MRI versus enhanced MRI: lesion visualization subject scores, diagnostic confidence, image quality, and increased signal intensity and signal-to-noise ratio
  - Unenhanced MRI versus paired or enhanced MRI: lesion visualization, intra-reader and inter-reader agreement in lesion visualization, change in lesion count, and impact on subject management

Major Findings

For all three readers, paired and enhanced MRI were statistically superior to unenhanced MRI alone in lesion visualization for all three morphology elements. Further:

- Two of three readers found paired images to be of significantly higher quality than unenhanced images.
- Higher image quality increased diagnostic confidence.
- Intra-reader and inter-reader agreement was higher for paired images than for unenhanced images.
- No significant difference was observed for lesion counts and clinical management.

To confirm the positive study findings, a new prospective study was conducted. The overall study design was similar to that of the original Study DGD-03-44-A but with study objectives and endpoints of the re-read Study DGD-44-051. The new study included pediatric subjects and the use of a currently approved MRI contrast agent as internal validation, as further described below.

Study DGD-44-050

Safety and efficacy evaluation of Dotarem® in magnetic resonance imaging (MRI) in patients with central nervous system (CNS) lesions (SENTIO Study)

The primary objective of this study was to demonstrate that enhanced MRI using Dotarem® is superior to unenhanced MRI in visualization (border delineation, internal morphology, and contrast enhancement) of CNS lesions with disrupted BBB and/or abnormal vascularity. This three-arm study was conducted over 14 months (September 2010 to November 2011) at 46 internal sites: 15 in United States; six each in France and Germany; three each in Argentina, Austria, Chile, and Spain; two each in Brazil, Italy, and Korea; and one in United Kingdom.

A total of 402 subjects were enrolled: 364 adults randomized into two blinded groups, either Dotarem® (245 adults) or Magnevist® (119 adults) and 38 children enrolled (not randomized) into the third open-label group (Dotarem® only). Subjects served as their own control for both Dotarem® and Magnevist® evaluations; the study was powered to support the use of Magnevist® for internal validation rather than as active control.

Both contrast agents were administered as an intravenous bolus (0.2 mL/kg). Within 28 days of screening, unenhanced MRI was followed immediately by enhanced MRI using either contrast agent. Images were read by three off-site (independent) and one on-site reader. All three arms were single-blinded for MRI interpretation (unenhanced versus enhanced), and the two adult arms were double-blinded for contrast agent identity.

Subject Selection

- Inclusion criteria
  - Adult and pediatric subjects (age ≥ two years) scheduled for enhanced MRI of the CNS
  - At least one known or suspected CNS lesion with disrupted BBB and/or abnormal vascularity
  - Women of child-bearing potential: effective contraception, surgically sterile, or post-menopausal
- Exclusion criteria
  - Acute or chronic renal insufficiency (Grade IV or V, glomerular filtration rate < 30 mL/min/1.73 m²)
  - Receipt of contrast agent within three days or anticipated receipt within 24 hours
  - Contraindication to MRI or known allergy to gadolinium chelates

Endpoint Assessment

- Co-primary endpoints and analyses in adult subjects: Difference in morphology score between two MRI modalities, unenhanced MIR alone versus paired MRI (unenhanced and enhanced read together), for each of three pre-defined morphology elements of lesion visualization.
  - The three pre-defined morphology elements consisted of border delineation, internal morphology, and degree of contrast enhancement.
  - For each subject, up to five largest lesions were selected. For each lesion, the three morphology elements were scored using a three-point scale: unevaluable 0, inadequate 1, and adequate 2.
  - For each morphology element, a subject score was calculated as the sum of all lesion scores. The difference in subject score between unenhanced and paired MRI served as a co-primary endpoint.
  - Dotarem® was to be considered effective if supported by a statistically significant difference in subject score for all three morphology elements in at least two of the three off-site blinded readers.
- Secondary endpoints and analyses: Adult primary endpoints and analyses applied to pediatric subjects (Dotarem® only), and the following new evaluations (comparisons at subject and lesion levels):
  - Comparison of unenhanced versus enhanced/paired MRI: lesion visualization, diagnostic confidence, image quality, signal intensity, signal-to-noise ratio, intra-reader and inter-reader agreement, and lesion count
  - Comparison of contrast agents (Dotarem® versus Magnevist®): lesion visualization, lesion number and location, image quality, diagnostic confidence, and signal intensity
- Subject Populations
  - Intent-to-treat (ITT): all enrolled subjects
  - Evaluable: valid primary co-endpoint assessments
  - Per-protocol: evaluable without major protocol violations
  - Safety: injection of either contrast agent
- Clinical safety: AEs, injection site tolerance, vital signs, ECG findings, and laboratory results as evaluated at 24 ± 4 hours after contrast agent administration

Major Findings

- For all readers, lesion visualization (co-primary endpoints), image quality, signal-to-noise ratio, and diagnostic confidence were superior with paired or enhanced MRI than with unenhanced MRI. Read-results were not highly reproducible (moderate intra-reader and poor inter-reader agreement).
- Efficacy and safety results were not appreciably different between the two contrast agents (Dotarem® or Magnevist®), and efficacy results were consistent between adults (statistically significant) and children (statistically non-significant).

II. INSPECTION RESULTS

The inspection outcomes are shown in the table below. For this new molecular entity (**NME**) NDA, the pivotal Studies DGD-44-050 and DGD-44-051 were audited at good clinical practice (**GCP**) inspections of: (1) the sponsor (Guerbet, LLC), (2) the imaging contract research organization (**CRO**) (b) (4) and (3) two clinical study sites in Study DGD-44-050 (Boys, Site 0702; Burrowes, Site 0719).

The two clinical study sites in Study DGD-44-050 were selected based on: (1) being a pediatric site (Site 0719 only), (2) no prior FDA inspection history (both sites), and (3) large numbers of reported AEs and protocol violations relative to the numbers of subjects enrolled (both sites):

- Site 0702: 0.93 AEs and 1.3 protocol violations per (adult) subject reported in the NDA, with 16 of 22 (73%) of protocol violations for one Subject 070215 (40 year old woman) and only one of 16 total AEs at this site (6%) seen in the same Subject 070215 (mild hyperkalemia, uneventful resolution, and thought to be unrelated to the study medication)
- Site 0719: 1.0 AEs and 1.3 protocol violations per (pediatric) subject reported in the NDA, no notable occurrence pattern for AEs or protocol violations.

	Inspected Entity	Studies, Sites, & Subjects	Inspection Dates & Outcome
1	Guerbet, LLC 1185 West 2nd Street Bloomington, IN 47403	DGD-44-050, DGD-44-050, & DGD-03-44-A all sites & subjects	Jan 7 - 10, 2013 final outcome pending (preliminary NAI)
2	(b) (4)	DGD-44-050 & DGD-44-051 all sites & subjects	Jan 7 - 14, 2013 final outcome pending (preliminary NAI)
3	Gregory Boys, MD Clinical Trials of Texas, Inc. 7940 Floyd Curl Drive, Suite 700 San Antonio, Texas 78229	DGD-44-050, Site 0702 18 adult subjects enrolled, 17 given study medication	inspection pending
4	Delilah Burrowes, MD Children's Memorial Hospital 2300 Children's Plaza, Mailbox 9 Chicago, Illinois 60614	DGD-44-050, Site 0719 7 pediatric subjects	Dec 31, 2012 - Jan 4, 2013 final outcome pending (preliminary NAI)

NAI = no action indicated (no significant deviations from regulations observed); VAI = voluntary action indicated (significant deviations from regulations observed); OAI = official action indicated (significant deviations from regulations and/or data unreliable warrant official regulatory action)

Pending: This preliminary outcome classification is based on information on Form FDA 483 and communication with the field investigator; final establishment inspection report has not been received from the field office and OSI's complete review of the report remains pending as of this clinical inspection summary.

Guerbet, LLC (Sponsor)

a. What was inspected:

- Applicable GCP regulations, to include adequacy of the sponsor's: (1) standard operating procedures (**SOPs**) for AE reporting and selecting (and monitoring) clinical study sites and CROs (and adherence to the SOPs); and (2) data management, including robustness of electronic controls over database interface, compatibility, and audit
- Test article handling and accountability, primary CRO contracts, Forms FDA 1572, and financial disclosure records
- Verification of the co-primary efficacy data (morphology scores for unenhanced and paired MRI) received from (b) (4) comparison review of NDA data listings and CRFs

b. General observations:

- Form FDA 483 was not issued. The sponsor's records indicated adequate control over the various aspects of the audited studies. There was no evidence of image unblinding or biased image interpretation. No discrepancies or underreporting of protocol violations were observed. Drug accountability records were adequate.
- One observation was verbally discussed. The observation was not necessarily a GCP deficiency and therefore was not cited on Form FDA 483.
  - The sponsor could have but did not notify FDA that a non-compliant study site (Site 0802, Study DGD-44-050) was prohibited from further subject enrollment (after enrolling 6 subjects) upon discovery of significant GCP non-compliance at a routine sponsor monitoring visit.
  - The affected efficacy data were appropriately reported in the NDA as not having been collected per the study protocol. The site was not terminated so that pending safety visits for the 6 subjects already enrolled (and given the study medication) could be completed.

  Reviewer's Comments:

  In preliminary communication with the FDA field investigator, the many protocol violations at this site did not appear serious enough (as noted in the sponsor's monitoring report) to warrant discontinuation of subject enrollment; however, the number (rate) of protocol violations may have been unacceptable to the sponsor.

  FDA may conduct an independent for-cause inspection of this site (if the deficiencies are deemed sufficiently serious) upon receipt and review of the final establishment inspection report.

c. Assessment of data integrity: The data reported in the NDA appear reliable.

Note: Observations noted above for this sponsor inspection are based on Form FDA 483 and preliminary communications with the field investigator.

(b) (4)

a. What was inspected:

- Scope of inspection:
  - Evaluation of adherence to: (1) contractual agreement with the sponsor; (2) standard operating procedures (**SOP**) for image processing, blinded image interpretation, and data management; (3) study protocols; and (4) applicable GCP regulations
  - Verification of efficacy data and robustness of database controls

- Efficacy data verification (co-primary endpoints of lesion border delineation, internal morphology, and contrast enhancement): three scans (pre/post/paired imaging) were reviewed for 10 subjects in Study DGD-44-051 and for 15 subjects in Study DGD-44-050.

b. General observations:

- No significant deficiencies were observed and a Form FDA 483 was not issued. The CRO adhered adequately to contract with sponsor, SOPs, study protocols, and applicable GCP regulations.
- The primary efficacy endpoint data were verifiable. The efficacy data reported in the two NDA supplements were compared against the corresponding data on CRFs. No discrepancies were noted.
- There was no evidence of reader unblinding or other biases in reading images or reporting the results. A review of the IRC charter compliance records revealed no significant deviations.
- Any necessary corrective action was implemented using a Data Clarification Form issued to the study site that performed the MRI. A review of a random sampling of issued forms indicated appropriate quality controls and procedures.
- The database controls appeared to be adequate in preventing data entry errors and in tracking changes to existing data.
  - Time stamping of data was confirmed in the firm's software system (BioTrack). Individual readers had password-protected access to the database when entering clinical data. Audit trails could be tracked for the readers.
  - Once the entered data were finalized, it was technically not possible to re-edit or retrieve the information; access to the reader-saved files was limited to frozen screenshots.

c. Assessment of data integrity: The data reported by (b) (4) appear reliable.

Note: Observations noted above for this CRO inspection are based on Form FDA 483 and preliminary communications with the field investigator.

Delilah Burrowes, M.D. (Study DGD-44-050, Site 0719)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations.
- Data verification: primary and major secondary endpoints, AEs, subject randomization, protocol deviations, and subject discontinuations
- Subjects: 29 subjects were screened, 7 enrolled, and 7 completed the study. Subject records for all enrolled subjects were reviewed in detail, to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
  - This study site was an open-label single-arm pediatric site; all subjects at this site were pediatric subjects (age 3 - 16 years) given open-label Dotarem® (not randomized and blinded between Dotarem® and Magnevist® arms).

- Informed assent was appropriately obtained for each subject according to applicable regulations. Adherence to the study protocol was adequate, including subject eligibility determination, test article disposition and accountability, subject randomization, and the study blind. Protocol violations that were reported to the sponsor (and subsequently reported by the sponsor in the NDA as protocol violations) were not cited on Form FDA 483.

- Verbal discussion (not cited on Form FDA 483): For one of two shipments of the study medication, the temperature range during shipment was not recorded.

  Reviewer's Comment:

  In general, the study results at this site support Dotarem® efficacy, safety, and intact Dotarem® product quality. However:

  - *In one Subject 071907, the image quality did not improve with Dotarem® use; it is unclear if imaging could have improved also for this subject with more rigorous attention to product handling, including documentation of temperature control during shipment.*
  - *The numbers of AEs and protocol violations were higher than expected relative to the number of subjects at this site. Not documenting the temperature range during shipment may be considered an unreported protocol violation, which may or may not have contributed subtly to an increase in AE rate and/or decreased product efficacy.*

  Given the general context (inspection and site-specific NDA data), the observed deficiency nonetheless appears unlikely to have importantly impacted the study data or subject safety. If the data were impacted, Dotarem® would be more effective and safer than is supported by the actual data, and therefore the data from this site may be considered reliable.

- Source records were neat, well organized, complete, and matched corresponding CRFs. The on-site (non-primary) efficacy (lesion morphology, unenhanced versus paired MRI) appeared to have been assessed by qualified personnel, under the study blind and according to the study protocol.

c. Assessment of data integrity: Data from this study site appear reliable.

Note: Observations noted above for this Site 0719 of Study DGD-44-050 are based on preliminary communications with the field investigator.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

The conduct of three pivotal Dotarem® studies (described above, *Background*) was inspected for GCP compliance at three sites: Guerbet (sponsor), (b) (4) (imaging CRO), and clinical study Site 0719 of Study DGD-44-050 (Burrowes). The inspection of a fourth site, clinical study Site 0702 in Study DGD-44-050 (Boys) has not been completed as of this clinical inspection summary report.

At all three completed inspections, no significant deficiencies were observed and a Form FDA 483 was not issued. The studies appeared to have been conducted in accordance with the study protocol, established SOPs, and applicable GCP regulations. The efficacy data reported in the NDA were verifiable against the corresponding CRFs and source records. The data reported by the sponsor in the NDA appear reliable as evaluated at the three of four inspections completed to date.

The numbers of AEs and protocol violations reported at the two clinical study sites were higher than expected from the relatively small number of subjects. The reasons for the AE and protocol violation rates remain unclear. The inspectional findings (at one of two clinical sites) indicate due diligence in study conduct, including AE and protocol violation monitoring and reporting.

Note: The inspection of Site 0702 in Study DGD-44-050 (Boys) has not been completed as of this interim clinical inspection summary report. For the three completed inspections, the establishment inspection reports have not been received from the field office and the final inspection outcomes remain pending. The observations noted above are based on preliminary communications with the field investigators. A final inspection summary will be forwarded to DMIP after completion of all inspections.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

JONG HOON LEE
01/24/2013

SUSAN LEIBENHAUT
01/25/2013

SUSAN D THOMPSON
01/25/2013

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	204781
Brand Name	DOTAREM
Generic Name	Gadoterate meglumine
Sponsor	Guerbet
Indication	To detect and visualize areas with disruption of the blood bran barrier (BBB) and/or abnormal vascularity
Dosage Form	Intravenous injection
Drug Class	Paramagnetic macrocyclic contrast agent
Therapeutic Dosing Regimen	0.1 mmol/kg bolus injection
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	NA
Submission Number and Date	SDN 001 September 20, 2012
Review Division	DMIP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes in mean QT interval (>20 ms) were detected in this trial following gadoterate meglumine 0.1 mmol/kg i.v. bolus followed by an injection of 0.2 mmol/kg 20 minutes later. The largest upper bound of the 2-sided 90% CI for the mean change from placebo and baseline adjusted was 6.7 ms observed 5 minutes post-dose. Because of the lack of a positive control in the study to demonstrate assay sensitivity, the results should be interpreted as having ruled out an effect of about 20 ms.

In this randomized, double-blinded, crossover study, 40 patients received placebo and gadoterate meglumine 0.1 mmol/kg i.v. bolus followed by an injection of 0.2 mmol/kg 20 minutes later. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Gadoterate Meglumine (0.1 mmol/kg)

Treatment	Time (minutes)	ΔΔQTcF (ms)	90% CI (ms)
Gadoterate Meglumine	5	3.3	6.7

According to the proposed product label, a single dose of 0.1 mmol/kg is being proposed as the therapeutic dose. The second injection of 0.2 mmol/kg used in this study is expected to achieve C_{max} approximately 2-fold that of the therapeutic dose. Therefore, supratherapuetic exposures were achieved in this study. Renal impairment is known to prolong the half-life of gadoterate meglumine, but large increases in C_{max} are not anticipated.

2 PROPOSED LABEL

QT-IRT recommends the following language in the label. Our recommendations are suggestions only. We defer final labeling decisions to the review division.

12.6 Cardiac Electrophysiology

The QT interval prolongation potential of DORATEM was assessed in 40 patients who received 0.2 mL/kg intravenous bolus followed by 0.4 mL/kg twenty minutes later. No large changes in the mean QTc interval (i.e., >20 ms) from baseline were detected in the study. However, a small increase in the mean QTc interval (i.e., <10 ms) cannot be excluded because of study design limitations.

3 BACKGROUND

3.1 PRODUCT INFORMATION

DORATEM (gadoterate meglumine) is a small cyclic molecule complex holding a gadolinium ion.

3.2 MARKET APPROVAL STATUS

DORATEM is approved for marketing in Europe (more than 20 years) and Japan.

3.3 PRECLINICAL INFORMATION

No cardiotoxicity was described, but neither do there appear to have been specific cardiotoxicity studies or a hERG assay.

3.4 PREVIOUS CLINICAL EXPERIENCE

Among over 2800 subjects in controlled trials adverse reactions are common, but cardiovascular events are rare. Safety studies in >100000 subjects revealed no cardiac adverse effects. ECGs have been collected in some safety studies, but no systematic effects on ECG intervals or rhythm disturbances have been noted.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of gadoterate meglumine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report DGD-44-039 for gadoterate meglumine, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Gd-DOTA (DOTAREM®): EVALUATION OF THE ELECTROCARDIOGRAPHIC SAFETY IN PATIENTS

4.2.2 Protocol Number

DGD 44-039A

4.2.3 Study Dates

Study Start: July 9, 2003

Study End: September 9, 2003

4.2.4 Objectives

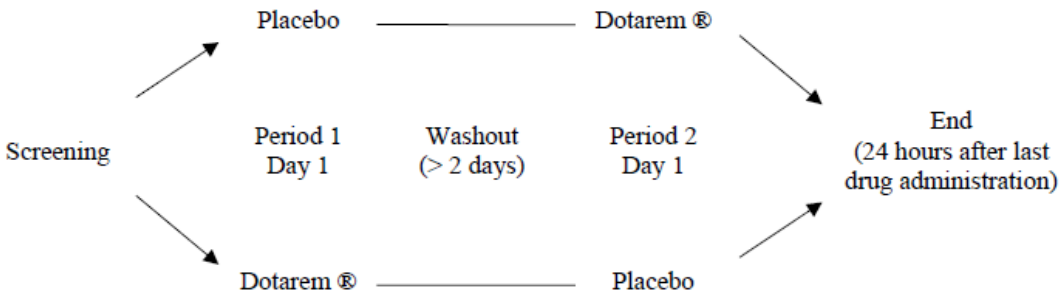
To evaluate the electrocardiographic safety of gadoterate megluimine in patients after bolus i.v. administration

4.2.5 Study Description

4.2.5.1 Design

This was a double-blind, crossover, placebo controlled study described in Figure 1.

Figure 1: Study Design



Source: Study Report, Figure 9.1-1, Page 15.

4.2.5.2 Controls

The Sponsor used placebo control.

4.2.5.3 Blinding

This was a double-blind study.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There are two treatment arms in this study

- Placebo
- Gadoterate meglumine: 0.1 mmol/kg i.v. bolus followed by an injection of 0.2 mmol/kg 20 minutes later

4.2.6.2 Sponsor's Justification for Doses

The cumulative dose of 0.3 mmol/kg was chosen as this dose corresponds to the highest one used in clinical practice in Europe.

Reviewer's Comment: According to the proposed product label, a single dose of 0.1 mmol/kg is being proposed as the therapeutic dose. The second injection of 0.2 mmol/kg used in this study is expected to achieve C_{max} approximately 2-fold that of the therapeutic dose. Therefore, supratherapuetic exposures were achieved in this study. Renal impairment is known to prolong the half-life of gadoterate meglumine, but large increases in C_{max} are not anticipated. Therefore, the doses used in this study are acceptable.

4.2.6.3 Instructions with Regard to Meals

Gadoterate meglumine is administered via i.v. bolus. Therefore, interaction with food is not expected.

4.2.6.4 ECG and PK Assessments

ECGs were collected 15, 10 and 5 minutes pre-dose and 1, 5, 10, 21, 30 minutes and 1, 12 and 24 hours following the first injection. PK assessments were not included in this study.

Reviewer's Comment: The timing of ECGs was adequate to capture peak effects at the end of bolus and delayed effects over 24 hours.

4.2.6.5 Baseline

Baseline was defined as the mean of three measured values before the first injection.

4.2.7 ECG Collection

Twelve-lead cart ECGs were used for safety evaluations and 12-lead Holters were used to obtain records for formal analysis. QT intervals were obtained from three beats at nominal time points.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

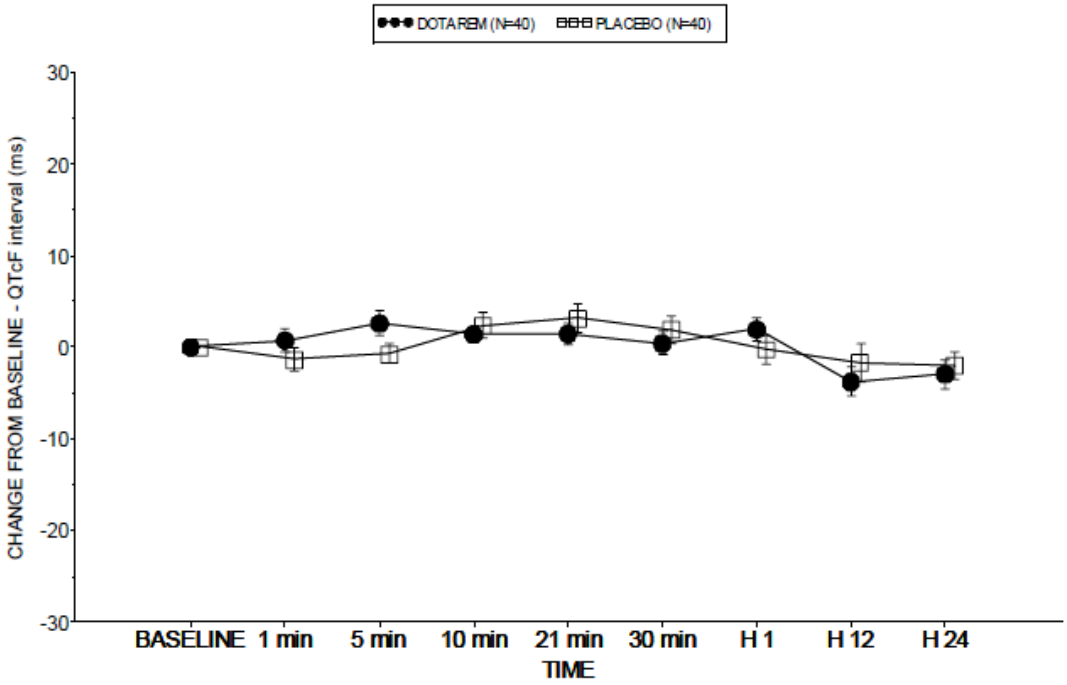
Forty healthy volunteers age 19 to 75, 50% female, participated in the study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The mean change from baseline ΔQTcF (±SD) for gadoterate meglumine was 1.5 ± 7.4 ms. The mean change from baseline ΔQTcF (±SD) for placebo was 3.1 ± 10.3 ms. This time course of ΔQTcF is presented in Figure 2. The difference between gadoterate meglumine and placebo for maximal QTcF increase from baseline was -0.68 ms with a 95% confidence interval of [-4.07; 2.72].

Figure 2: Time course of ΔQTcF



Source: Study Report, Figure 12.5-6, Page 44.

Reviewer's Comments: The reviewer's analysis is described in section 5.2.

4.2.8.2.2 Categorical Analysis

There were no QTcF values greater than 480 ms and no ΔQTcF values greater than 60 ms in any of the patients receiving gadoterate meglumine or placebo. A QTcF value greater than 450 ms occurred in 3 patients following both placebo and gadoterate meglumine and in 3 patients following gadoterate meglumine only.

◆ HR categorical analysis :
HR values were analyzed in terms of HR ≥ 100 bpm associated with an increase from baseline ≥ 20 bpm and HR value < 40 bpm associated with a decrease from baseline ≥ 20 bpm. No out-of-range HR value was observed.
♦ QRS ≥ 120 ms
One patient presented QRS values above 120 ms before administration and after both treatment administration : Patient 1037 (male, 40 year old).
♦ PR ≥ 220 ms
One patient presented PR interval values above 220 ms before administration

4.2.8.3 Safety Analysis

All randomized subjects completed study. Adverse events were not serious and none appeared to of cardiac origin.

4.2.8.4 Clinical Pharmacology

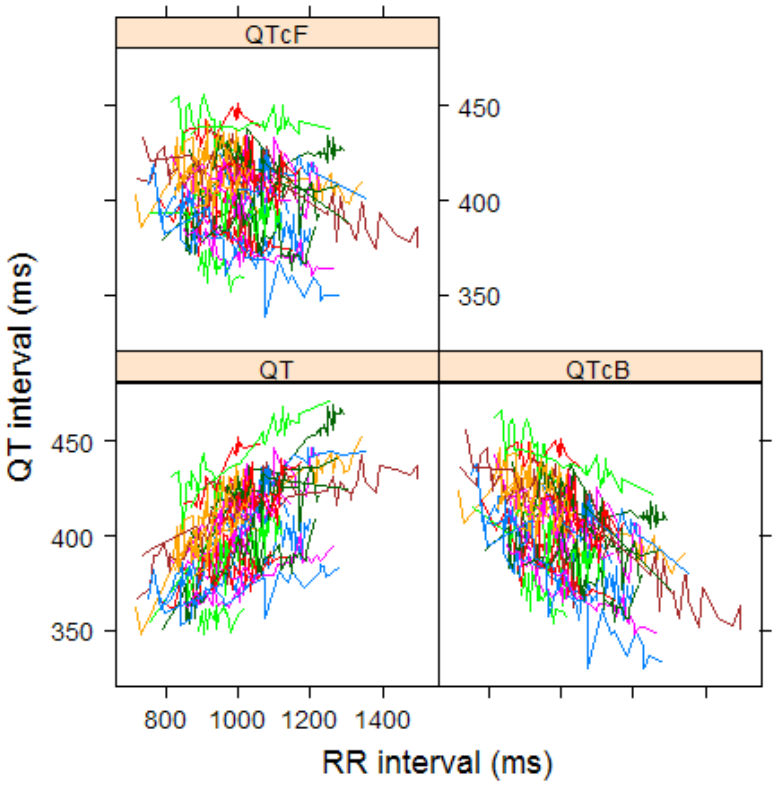
Pharmacokinetic data was not collected in this study.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the analysis. Ideally, a good correction would result in no relationship between QTc and RR intervals. The relationship between different correction methods and RR is presented in Figure 3. QTcF was chosen as the correction method for the study.

Figure 3: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Gadoterate Meglumine

The reviewer used a mixed model to analyze QTcF change from placebo and baseline adjusted (ΔΔQTcF). The results are listed in Table 2. The largest bound of the 2-sided 90% CI for the mean difference between gadoterate meglumine and placebo was 6.69 ms at 5 minutes post-dose.

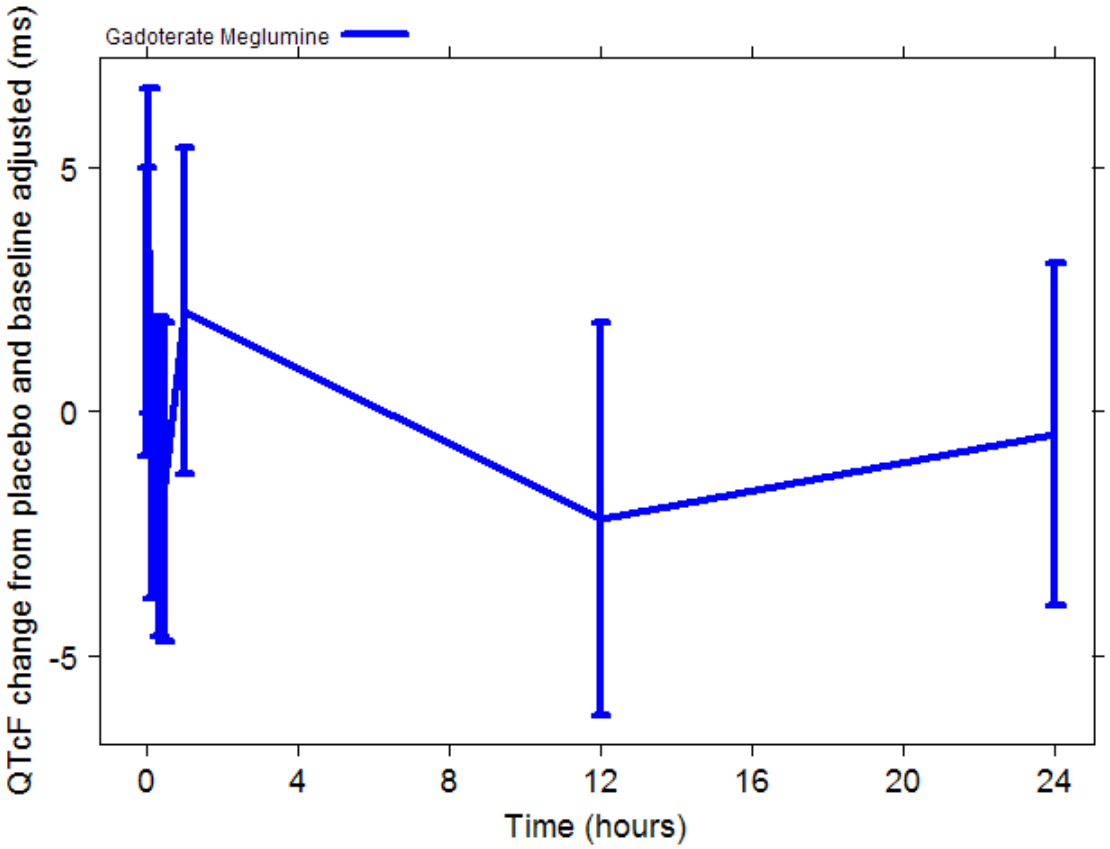
Table 2: Analysis Results of ΔΔQTcF for Gadoterate Meglumine

	ΔΔQTCF		
Time	**Mean (ms)**	**Standard Error (ms)**	**90% CI**
1 min	2.03	1.79	(-1.00, 5.06)
5 min	3.28	2.02	(-0.13, 6.69)
10 min	-0.99	1.72	(-3.89, 1.91)
21 min	-1.34	1.99	(-4.70, 2.02)
30 min	-1.45	1.98	(-4.79, 1.89)
1 hour	2.06	2.03	(-1.36, 5.47)
12 hour	-2.19	2.45	(-6.33, 1.94)
24 hour	-0.47	2.13	(-4.06, 3.13)

5.2.1.2 Graph of ΔΔQTcF Over Time

Figure 4 displays the time profile of ΔΔQTcF for gadoterate meglumine.

Figure 4: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.3 Categorical Analysis

Table 3 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 3: Categorical Analysis for QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms	
Treatment Group	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
Gadoterate Meglumine	40	450	38 (95%)	448 (99.6%)	2 (0.4%)	2 (0.4%)
Placebo	40	455	39 (97.5%)	451 (99.1%)	1 (2.5%)	4 (0.9%)

Table 4 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 4: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Gadoterate Meglumine	40	328	40 (100%)	328 (100%)	0 (0%)	0 (0%)
Placebo	40	329	39 (97.5%)	328 (99.7%)	1 (2 5%)	1 (0.3%)

5.2.2 PR Analysis

The outlier analysis results for PR are presented in Table 5.

Table 5: Categorical Analysis for PR

	Total N		PR ≥ 200 ms	
Treatment Group	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)
Gadoterate Meglumine	40	450	8 (20%)	49 (10.9%)
Placebo	40	455	7 (17.5%)	51 (11.2%)

5.2.3 QRS Analysis

The outlier analysis results for QRS are presented in Table 6.

Table 6: Categorical Analysis for QRS

	Total N		QRS ≥ 110 ms	
Treatment Group	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)
Gadoterate Meglumine	40	450	2 (5%)	15 (3.3%)
Placebo	40	455	1 (2.5%)	11 (2.4%)

5.3 CLINICAL ASSESSMENTS

5.3.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

There was no finding warranting close monitoring during or following drug administration.

5.3.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appear acceptable.

5.3.3 PR and QRS Interval

No clinically significant effect was seen on PR or QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	0.1 mmol/kg
Maximum tolerated dose	NA
Principal adverse events	The most frequent (≥ 0.2%) adverse reactions associated with Dotarem in clinical studies were nausea, headache, injection site pain, injection site coldness, burning sensation, rash, and fatigue.
Maximum dose tested	Single dose : 0.1 mmol/kg Multiple dose : 0.1 mmol/kg followed by 0.2 mmol/kg twenty minutes after.
Exposures achieved at Maximum dose tested	Single dose AUC $_{0\text{-inf}}$: 867 to 1061 µmol.l^{-1}.h [#] C_{max} : 799 to 837 µmol.l^{-1} Multiple dose AUC $_{0\text{-t}}$: 2897 to 3015 µmol.l^{-1}.h [#] C_{max} 2nd injection : 1778 to 2166 µmol.l^{-1}
Range of linear PK	Linear across dose range studied
Accumulation at steady state	NA
Metabolites	Gadoterate meglumine is not metabolized
Absorption	NA
Distribution	Vd = 11 to 17 L [#] %bound : < 4% (in vitro)
Elimination	Route : kidneys via glomerular filtration T ½ (h) =1.3 to 2.0 [#] Clp (mL/min) = 107 to 140 [#]
Intrinsic factors	Age : not specifically studied but see renal impairment below

	Sex : no relevant difference Race : not studied but no race effect expected due to the lack of protein binding and metabolism Hepatic impairment : not studied but no effect expected due to the lack of metabolism Renal impairment: elimination is proportionally decreased with the degree of renal impairment. Effect of renal impairment was studied comparing healthy volunteers (group 1), patients with moderate renal impairment (creatinine clearance between 30 and 60 mL/min – group 2), and patients with severe renal impairment (creatinine clearance between 10 and 30 mL/min – group 3). Elimination half-life was 1.6 ± 0.2 hrs, 5.1 ± 1.0 hrs and 13.9 ± 1.2 hrs in groups 1, 2 and 3, respectively. AUC_{exp} was 870 ± 80 hrs, 3013 ± 645 hrs and 8122 ± 665 hrs in groups 1, 2 and 3, respectively. Total clearance was 108.3 ± 7.8 hrs, 40.0 ± 8.8 hrs and 13.8 ± 0.6 hrs in groups 1, 2 and 3, respectively.
Extrinsic factors	Drug interactions and food effects: Dotarem is an extracellular gadolinium-based contrast agent which is rapidly distributed in the extracellular space after administration. It is not metabolized and is eliminated by the kidneys via glomerular filtration. The extrarenal elimination is negligible. There is no potential risk for drug-drug or drug-food interactions. No relevant drug-drug or drug-food interactions have been identified in clinical trials or in post marketing experience, although no specific studies have been carried-out.
Expected high clinical exposure scenario	Such scenario is very unlikely due to the size of containers proposed in the NDA and because Dotarem will be administered only by healthcare professionals.

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/s/

KEVIN M KRUDYS
12/13/2012

NORMAN L STOCKBRIDGE
12/13/2012