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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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Statistical Review and Evaluation
Clinical Studies

NDA/BLA	NDA 204781 s001
Drug Name:	DOTAREM (gadoterate meglumine) Injection
Proposed Indication(s):	DOTAREM is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
Applicant:	Guerbet LLC
Date(s):	NDA Submission: 4 November 2016 PDUFA Date: 27 August 2017
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1. EXECUTIVE SUMMARY

Dotarem (gadoterate meglumine) 0.5 mmol/mL has been approved by the FDA on 20th March 2013 (NDA 204-781) to be used in the magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. The FDA requested to collect additional data in the 0-23 month's age group. This NDA was submitted based on based on FDA recommendations to conduct two additional studies (clinical and PK) in the 0-23 month's age group.

Efficacy of Dotarem® in the CNS indication in pediatric patients aged < 2 years was assessed in one pivotal open-label, single-group, non-randomized study including 28 patients evaluable for efficacy (DGD-44-063), 3 supportive studies collectively including 7 patients aged < 2 years (DGD-03-015, DGD-03-016 and DGD-03-029), and 7 supportive PMS observational studies collectively including 213 patients <2 years evaluable for efficacy.

The evaluation of Dotarem® efficacy in the pivotal study was based on the qualitative assessment of image quality and lesion visualization (border delineation, internal morphology, contrast enhancement) based on pre + post-contrast images compared to pre-contrast images.

The overall quality of images was considered "good" for 26 patients (92.9%) and "fair" for 2 patients (7.1%) with pre-contrast images while it was "good" for all patients with pre + post-contrast images.

CNS lesions were identified in 16 of these 28 patients on paired pre- and post-contrast images compared to 15 patients on pre-contrast images alone. For the three co-endpoints of lesion visualization, the sum of scores was calculated at patient level. Lesions (up to 5 largest) were scored using a 3-point scale for 3 co-endpoints (lesion border delineation, internal morphology and contrast enhancement).

- Border Delineation Score for a lesion:
  1 = None; 2 = Moderate; 3 = Clear and Complete
- Internal Morphology Score for a lesion:
  1= Poorly visible; 2 = Moderately visible; 3 = Sufficiently visible
- Contrast Enhancement Score for a lesion:
  1 = None; 2 = Weak; 3=Clear and Bright

In the 16 patients that had identifiable lesions, summed scores improved on paired pre- and post-contrast images compared to pre-contrast images in 8 out of 16 (50%) of patients for lesion border delineation, 8 of 16 (50%) of patients for lesion internal morphology, and 14 out of 16 (88%) patients for lesion contrast enhancement.

2. INTRODUCTION

DOTAREM is a gadolinium-based contrast agent and is approved (03/20/2013) for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. Guerbet LLC proposes to add pediatric patients less than 2 years of age including term newborn infants to the indication.

2.1 Overview

Dotarem® is a macrocyclic, ionic, gadolinium-containing contrast agent, an injectable solution administered by intravenous route and intended for diagnostic examinations carried out by MRI. Dotarem was developed by Guerbet in the 1980's and was first approved in France in 1989 for examinations of the central nervous system (CNS). Since this date, Dotarem has been approved in more than 70 countries worldwide.

2.1.1 Regulatory History

Dotarem (gadoterate meglumine) 0.5 mmol/mL has been approved by the FDA on 20th March 2013 (NDA 204-781) to be used in the magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. During this priority review, the data regarding pediatric patients under 2 years of age were considered insufficient to grant approval in the 0-23 months age group.

The FDA requested to collect additional data in the 0-23 month's age group. Two additional studies were conducted following the FDA recommendations.

- DGD-33-041 to collect non-clinical data in newborn to juvenile animals that model pediatric patients in this age group.
- DGD-44-063 to collect clinical and PK data in children 0-23 months of age who are referred for an MRI exam with contrast. This study was conducted in 2015 and is considered pivotal in the clinical development program of Dotarem® for CNS imaging in pediatric patients aged <2 years.

The requested studies have been conducted and Guerbet submitted a Supplemental New Drug Application (sNDA) on 4 November 2016 to extend the US registration of Dotarem for the pediatric population aged < 2 years.

2.2 Data Sources

Data and definition files were provided by the sponsor. The NDA in eCTD and SAS export files of these data are located at: \\CDSESUB1\evsprod\NDA204781\0042

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis provided by the sponsor were adequate.

3.2 Evaluation of Efficacy

3.2.1 Study Design

There was one pivotal study (**DGD-44-063) e**valuating the efficacy and safety in the 0-2 years old pediatric population. This study was an open-label, comparative (before and after injection of contrast agent), multicenter to evaluate the safety and efficacy of Dotarem® following single intravenous injection in pediatric patients aged up to 23 months who were referred for an MRI exam with contrast. The assessment of Dotarem efficacy was based on the combined use of pre-contrast and pre + post-contrast MRI and how it compared to the pre-contrast MRI alone. This methodological approach was similar to the one used in the 2 pivotal studies DGD-44-051 and DGD-44-050 (which included a pediatric arm), included in the 2012 NDA submission.

3.2.2 Objective, number of subjects and methodology

Non-randomized multicenter study DGD-44-063 recruited subjects ranging from term infants to 23 month-olds who were scheduled to undergo contrast enhanced MRI of any body region. A total of 51 patients were enrolled. Six out of 51 patients did not receive Dotarem® due to consent withdrawal (n=2), adverse event (n=2) or another reason (n=2). A total of 45 patients received Dotarem and completed study (PK and safety set). These were analyzed for PK and safety. Dotarem efficacy was evaluated in the subset of 28 patients who had CNS imaging.

One site-reader for each subject evaluated up to the five largest individual lesions on both pre-contrast images alone as well as paired pre- and post- contrast MRI images for the following endpoints:

- Overall image quality (3-point scale, poor/fair/good)

- Lesion Visualization/Assessment - Lesions (up to 5 largest) were scored using a 3-point scale for 3 co-endpoints (lesion border delineation, internal morphology and contrast enhancement).
  - Border Delineation Score for a lesion:
    1 = None; 2 = Moderate; 3 = Clear and Complete
  - Internal Morphology Score for a lesion:
    1= Poorly visible; 2 = Moderately visible; 3 = Sufficiently visible
  - Contrast Enhancement Score for a lesion:
    1 = None; 2 = Weak; 3=Clear and Bright

3.2.3 Demographic and Baseline Characteristics

Patient demographics are presented in Table 1. The 28 patients evaluable for efficacy included 15 boys and 13 girls. Mean age (SD) was 8.2 months (7.2), with 5 patients aged 0-1 month, 6 patients aged 1-3 months and 17 patients aged 3-23 months. Approximately half of the 45 analyzed patients presented with neoplasms (n=23, 51.1%), the most frequent being neuroblastoma (n=7, 15.6%). Nine patients (20.0%) presented with nervous system disorders, the most frequent being epilepsy (n=5, 11.1%)

Table 1: Subject Demographics and Baseline Characteristics (Pivotal Studies-Sponsor)

	All Analyzed Patients (n=45)	All Patients Evaluable for Efficacy (n=28)
Age (months)		
Mean (SD)	9.88 (7.36)	8.21 (7.19)
Median (min; max)	9.3 (0.0, 23.8	5.7 (0.0, 23.8)
Age (in categories), N (%)		
≤30 days	5 (11.1%)	5 (17.9%)
≥31 days and ≤90 days	9 ((20.0%)	6 (21.4%)
≥91 days and <2 years	31 (68.9%)	17 (60.7%)
Sex, N (%)		
Male	22 (48.9%)	15 (53.6%)
Female	23 (51.1%)	13 (46.4%)
Race, N (%)		
Black or African American	1 (2.2%)	1 (3.6%)
White	43 (95.6%)	27 (96.4%)
Other	1 (2.2%)	0 (0.0%)
Weight (kg)		
Mean (SD)	8.1 (3.1)	7.6 (3.5)
Median (min; max)	8 (3; 15)	7 (3; 15)
Height (cm)		
Mean (SD)	68.8 (11.5)	66.8 (12.3)
Median (min; max)	71 (47; 87)	64 (47; 87)
Body Mass Index (kg/m²)		
Mean (SD)	16.5 (2.7)	16.1 (3.2)
Median (min; max)	17 (12; 25)	16 (12; 25)
MRI Indication, N (%)		
CNS	28 (62.2%)	28 (100.0%)24
-Brain (intracranial)	24	24
-Spine	7	7
-Associated tissues (head and neck)	4	4
Whole Body	4(8.9%)	1 (3.6%)
MSK	4(11.1%)	1 (3.6%)
Abdomen	7(15.6%)	1 (3.6%)
Other	7(15.6%)	0 (0.0%)
Total Volume of Dotarem Injected (mL)		
Mean (SD)	1.6 (0.6)	n.p.
Median (min; max)	2 (1;3)	n.p.

Abbreviations: CNS, central nervous system; max, maximum; min, minimum; MRI, magnetic resonance imaging; MSK: musculoskeletal; n.p., not provided; SD, standard deviation.

3.3 Efficacy Assessment (Pediatric < 2 Years) - Results of the Pivotal Study

The evaluation of Dotarem® efficacy in the pivotal, open-label, non-randomized, single-group study was based on the qualitative assessment of image quality and lesion visualization (border delineation, internal morphology, contrast enhancement). Only indication-specific visualization of actual CNS lesions was evaluated rather than including normal vessels or other body areas. Analysis on per lesion level increases the evaluated sample size.

3.3.1 Identification of Lesions (Pivotal Study):

- The number of lesions detected per patient ranged from 0 to 11, with a median of 1 lesion per patient.

- Lesions were identified in 15 of 28 subjects on pre-contrast images and 16 of 28 subjects on paired images

- In individual subjects with lesions, lesion number ranged from 1 to 11
  - **Majority** of these subjects had 1 lesion (62.5%)
  - **Pre-contrast images**: total of 34 lesions in 15 subjects
    - **28 evaluated lesions**
  - **Paired images**: total of 36 lesions in 16 subjects
    - **30 evaluated lesions -** 20 brain, 4 spine, 6 other head/neck
  - The number of subjects with lesions detected was 16 out of 28 efficacy population. There is also a potential referral bias. Single site-reader, no blinding to patient information or study purpose, qualitative rating scales could contribute to potential bias.

3.3.2 Quality of Images (Pivotal Study):

- Pre- and post-contrast images were rated as assessable in all 28 out of 28 CNS subjects by site readers

  – Pre-contrast Images - overall quality:
    - Good for 26 patients (92.9%)
    - Fair for 2 patients (7.1%)

  – Pre+ post-contrast Images – overall quality:
    - Good for all 28 good

3.3.3 Lesion Level Analysis (Pivotal Study)

For the three co-endpoints of lesion visualization (border delineation, internal morphology, contrast enhancement), the analysis was performed at lesion level (considering up to 5 largest lesions per patient) and at patient level (summing the scores for up to 5 lesions as well).

Table 2 provides analysis at the lesion level for all patients evaluable for efficacy (N=28). At lesion level, an improvement is noted with pre + post-contrast images compared to pre-contrast images with more lesions having the higher score with pre + post-contrast images.

Table 2: Lesion Level Analysis

	Pre-contrast[a] (N=28 lesions)	Pre + Post-contrast (N=30 lesions[a])
Lesion Border Delineation Score		
1-None	2 (7.1%)	0 (0.0%)
2-Moderate	15 (53.6%)	8 (26.7%)
3-Clear and complete	11 (39.3%)	22 (73.3%)
Internal Morphology Score		
1- Poorly visible	5 (17.9%)	0 (0.0%)
2- Moderately visible	9 (32.1%)	7 (23.3%)
3- Sufficiently visible	14 (50.0%)	23 (76.7%)
Contrast Enhancement Score		
1-None	28 (100.0%)	3 (10.0%)
2-Weak	0 (0.0%)	4 (13.3%)
3-Clear and Bright	0 (0.0%)	23 (76.7%)

[a]Lesions identified in pre- and post-contrast images could be different.
No missing data.

3.3.4 Patient Level Analysis (Pivotal Study)

For the three co-endpoints of lesion visualization, the sum of scores was calculated at patient level. At patient level, the mean sum of scores was higher with pre + post- contrast images compared to pre - contrast images.

Table 3 displays mean sum of scores for lesion border delineation, lesion internal morphology and lesion contrast enhancement at patient level.

The patient level difference between pre + post contrast versus pre-contrast for 15 patients with lesions detected out of 28 patients in the mean sum of scores for lesion border delineation was 0.7 (95% confidence interval ranging from -0.02 to 0.37); for lesion internal morphology was 0.9 (95% confidence interval ranging from -0.24 to 0.58); and lesion contrast enhancement was 3.1 (95% confidence interval ranging from 0.81 to 5.39).

Table 3: Patient Level (Sum of Scores) Analysis

Sum of Scores	Pre-contrast (N=28 patients)	Pre + Post-contrast (N=28 patients)	Difference[a] (N=28 patients)
Number of Patients with Lesions Detected	N=15	N=16	N=15
Lesion Border Delineation Score Mean (SD) Median (min; max) 95% Confidence Interval (Mean)	 4.3 (3.7) 3 (2; 15) (2.43, 7.17)	 5.1 (4.0) 3 (2; 15) (3.14, 7.06)	 0.7 (1.0) 0 (0; 3) (-0.02, 0.37)
Internal Morphology Mean (SD) Median (min; max) 95% Confidence Interval (Mean)	 4.3 (3.9) 3 (1; 15) (2.33, 6.27)	 5.2 (4.3) 3 (2; 15) (3.09, 7.31)	 0.9 (1.6) 0 (0; 6) (-0.24, 0.58)
Contrast Enhancement Mean (SD) Median (min; max) 95% Confidence Interval (Mean)	 1.9 (1.5) 1 (1; 5) (1.14, 2.66)	 5.0 (4.5) 3 (1; 15) (2.80, 7.21)	 3.1 (3.2) 2 (0; 10) (0.81, 5.39)

Abbreviations: max, maximum; min, minimum; SD, standard deviation.

[a]Difference: Pre + Post-contrast minus Pre-contrast.

In the 16 patients that had identifiable lesions, summed reader scores were improved on paired pre- and post-contrast images compared to pre-contrast images in 8 out of 16 (50%) of patients for lesion border delineation, 8 of 16 (50%) of patients for lesion internal morphology, and 14 out of 16 (88%) patients for lesion contrast enhancement. To calculate the patient-level results, the following strategy was employed. Separately for each imaging visualization category of border delineation, internal morphology, and contrast enhancement, the summed scores for all lesions identified in each individual patient were categorized as either improved (numerically increased) or the same on each individual patient's combined pre- and post-contrast images compared to the same individual patient's pre-contrast images alone. Importantly, subject 330502, in whom lesions were only identified on post-contrast images, was regarded as improved in all three categories. The percentage of patients with score improvement in each category was reported as a percentage of the total of 16 patients who had identifiable lesions.

Efficacy results obtained in the patients aged <2 years were consistent with those obtained in the adult population and in older children.

3.3.5 Supportive Imaging Efficacy Studies:

- Three supportive open-label, single-group, non-randomized studies collectively including 7 subjects aged <2 years with Dotarem-enhanced CNS MRI. Narrative accounts of Dotarem confirming absence of a lesion or improving lesion visualization.

- Seven post-marketing observational studies collectively including 213 patients < 2 years with Dotarem-enhanced CNS MRI
    - Summaries provided for 2 largest PMS studies (each n=85)
    - Paired images rated without comparison to pre-contrast images
    - Almost all scans reported to have good or better image quality (98%, 99%) and as allowing a diagnosis (definitely normal or definitely abnormal) to be made (98%, 99%)

3.4 Evaluation of Safety

In the Pivotal study, there were no reported deaths. Of the 52 pediatric patients under 2 years of age the safety population of the pivotal study DGD-44-063 study, 6 (11.5%) general disorders and administrative site condition; 6 (11.5%) Pyrexia; 6 (11.5%) infections and infestations, 4 (7.7%) gastrointestinal disorders, 2 (3.8%) vomiting, 2 (3.8%) blood and lymphatic disorders, and 2 (3.8%) leukopenia.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The comparison of results in sub-populations is not applicable. There were no special groups identified by the clinical team.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Dotarem (gadoterate meglumine) 0.5 mmol/mL has been approved by the FDA on 20th March 2013 (NDA 204-781) to be used in the magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. The FDA requested to collect additional data in the 0-23 month's age group. This NDA was submitted based on based on FDA recommendations to conduct two additional studies (clinical and PK) in the 0-23 month's age group.

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