CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216986Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 19, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216986
Product Name and Strength:	Elucirem (gadopiclenol) Injection, 1.5 mmol/3 mL (0.5 mmol/mL), (b) (4) mmol/7.5 mL (0.5 mmol/mL), 5 mmol/10 mL (0.5 mmol/mL), 7.5 mmol/15 mL (0.5 mmol/mL), 15 mmol/30 mL (0.5 mmol/mL), 25 mmol/50 mL (0.5 mmol/mL), and 50 mmol/100 mL (0.5 mmol/mL)
Applicant/Sponsor Name:	Guerbet LLC (Guerbet)
OSE RCM #:	2022-152-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Guerbet LLC (Guerbet) submitted revised container labels, carton labeling, and case labeling on September 7, 2022 and September 14, 2022 for Elucirem (gadopiclenol) Injection under NDA 216986. We reviewed the revised labels and labeling for Elucirem (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and via email on September 2, 2022 and September 12, 2022.[a,b,c]

2 CONCLUSION

We note our review included a recommendation to revise the 30 mL and 50 mL pharmacy bulk package container labels to a monolayer label instead of the proposed multiple layer label. On

[a] Kane, D. Label and Labeling Review for Elucirem (NDA 216986). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAY 26. RCM No.: 2022-152.
[b] https://darrts.fda.gov/darrts/faces/ViewCommunication-task-flow/viewCommunication?_afrRedirect=1080814330203075&_afrPage=5
[c] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806855fe

September 1, 2022, Guerbet stated “Due to the extreme dimensional constraints of the available printing spaces on the monolayer labels for 30 mL and 50 mL Pharmacy Bulk Package (PBP) vials, it is currently not possible for Guerbet to use monolayer labels on both, 30 mL and 50 mL Pharmacy Bulk Package (PBP) vials.”. Given the space constraints on the 30 mL and 50 mL Pharmacy Bulk Package vial container labels, we find Guerbet’s proposal to use a multiple layered label acceptable. Thus, Guerbet LLC implemented all of our recommendations and we have no additional recommendations at this time.

18 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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/s/

DEVIN R KANE
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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 Pharmacovigilance and Epidemiology

Pharmacovigilance Memorandum

Date:	July 27, 2022
Reviewer:	Sarah Kang, PharmD, Safety Evaluator Division of Pharmacovigilance II (DPV II)
Team Leader:	Mallika Mundkur, MD, MPH DPV II
Product Names:	Gadolinium-based contrast agents
Subject:	Nephrogenic systemic fibrosis in the age group 6 years and younger
Application Type/Number:	Multiple (See Appendix A)
Applicant/Sponsor:	Multiple (See Appendix A)
OSE RCM #:	2022-1023

EXECUTIVE SUMMARY

In this review, the Division of Pharmacovigilance II (DPV II) searched the FDA Adverse Event Reporting System (FAERS) and published medical literature for cases of nephrogenic systemic fibrosis (NSF) in the pediatric population (**aged 6 years and younger**). On January 21, 2022, the Division of Imaging and Radiation Medicine (DIRM) received a New Drug Application (NDA 216986) for gadopiclenol, a macrocyclic gadolinium-based contrast agent (GBCA). The Applicant's proposed indication for the product is for use with Magnetic Resonance Imaging (MRI), (b) (4) lesions in the central nervous system (CNS) and body among adults and children aged 2 years and older. To help inform review of this application, on May 24, 2022, DIRM requested that DPV evaluate postmarket data for cases of NSF with use of any GBCA (including approved as well as withdrawn products) in the age group 6 years and younger.

From our search of FAERS and the published medical literature, we did not identify cases of NSF occurring with use of GBCAs among individuals aged 6 years and younger. However, we note important limitations of this analysis. We underscore the universal problems of spontaneous reporting databases such as FAERS, including but not limited to underreporting, as well as limited and variable quality of information in spontaneous reports. In addition, underreporting may be influenced by whether the event is labeled and how long the drug has been on the market. In this case, NSF is a known adverse event associated with GBCA use and GBCAs have been available for a long time; therefore, consumers and healthcare providers are less likely to report. Medicolegal pressures may prevent healthcare institutions from publishing cases related to NSF potentially resulting in underreporting of cases in the literature as well. In this review specifically, inadequate reporting regarding age could have also contributed to our inability to identify cases among individuals aged 6 years and younger.

Although we do not have specific recommendations resulting from this review, DPV will continue to monitor for postmarket reports of NSF in the pediatric population.

1 INTRODUCTION

In this review, the Division of Pharmacovigilance II (DPV II) searched the FDA Adverse Event Reporting System (FAERS) and published medical literature for cases of nephrogenic systemic fibrosis (NSF) in the pediatric population (**aged 6 years and younger**). On January 21, 2022, the Division of Imaging and Radiation Medicine (DIRM) received a New Drug Application (NDA 216986) for gadopiclenol, a macrocyclic gadolinium-based contrast agent (GBCA). The Applicant's proposed indication for the product is for use with Magnetic Resonance Imaging (MRI), (b) (4) lesions in the central nervous system (CNS) and body among adults and children aged 2 years and older. To help inform review of this application, on May 24, 2022, DIRM requested that DPV evaluate postmarket data for cases of NSF with use of any GBCA (including both approved as well as withdrawn products) in the age group 6 years and younger.

Of note, in the pediatric study[a] supporting this application, gadolinium retention was reported for 10 of 80 pediatric patients (detected from urine samples). However, no patients experienced suspected NSF or NSF-related symptoms (Bagheri 2022).

GBCAs

The primary categories of GBCAs are macrocyclic and linear (**Appendix A**). Macrocyclic GBCAs form cage-like structures with gadolinium ions enclosed in the complex, have lower dissociation constants[b] and are thought to be more stable than the linear GBCAs (Port et al. 2008, Rogosnitzky and Branch 2016). The American College of Radiology classified GBCAs into different groups (i.e., I, II and III) based on reported associations with NSF (**Table 1**).

Table 1. American College of Radiology Manual Classification of GBCA Relative to Frequency of NSF* (ACR 2021)

Group I Agents associated with the greatest number of NSF cases	Gadodiamide (L) Gadopentetate dimeglumine† (L) Gadoversetamide† (L)
Group II Agents associated with few, if any, unconfounded cases of NSF	Gadobenate dimeglumine (L) Gadobutrol (M) Gadoteric acid (M) Gadoteridol (M)
Group III Agents for which data remains limited regarding NSF risk, but for which few, if any unconfounded cases of NSF have been reported	Gadoxetate disodium (L)

*Adapted from American College of Radiology Committee on Drugs and Contrast Medi**a** (ACR 2021)
† Withdrawn from the U.S. market (See **Appendix A** for more detail)

[a] Study GDX-44-007 included pediatric patients aged 2 to 17 years. The primary objective of the study was to evaluate the pharmacokinetic profile of gadopiclenol.
[b] The higher the dissociation constant, the more likely free gadolinium is released into the circulation and tissues.

Table 1. American College of Radiology Manual Classification of GBCA Relative to Frequency of NSF* (ACR 2021)

Abbreviations: GBCA=Gadolinium-Based Contrast Agent; L=Linear; M=Macrocyclic; NSF=Nephrogenic Systemic Fibrosis

NSF

In 2006, two case series first described the association between GBCAs and NSF in patients with advanced kidney disease (Grobner 2006, Marckmann et al. 2006). As stated in an FDA safety communication, patients with impaired elimination of GBCAs (e.g., chronic kidney disease) are at "greatest risk" for developing NSF (FDA 2010). NSF in patients with kidney disease may be characterized by thickening and hardening of the skin overlying the extremities and trunk, and marked expansion and fibrosis of the dermis in association with $CD34^+$ fibrocytes (Rudnick et al. 2022). NSF can also affect muscle, joints and internal organs (e.g., lungs and heart) leading to functional disability and organ failure (Rudnick et al. 2022).

Although the exact mechanism explaining the occurrence of NSF with GBCAs is not known, the most accepted hypothesis is dissociation of gadolinium ions from the chelates in GBCAs in patients with kidney disease due to prolonged clearance time of the GBCAs. The free gadolinium may then bind with an anion (e.g., phosphate), resulting in insoluble precipitates and depositing in various tissues (Collidge et al. 2007, Abraham et al. 2008).

Regulatory History

In December 2009, FDA convened the Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to review data pertaining to the development of NSF in association with GBCAs and requested the committees' advice regarding measures to minimize the risk (FDA 2009a).

In preparation for the meeting, the Office of Surveillance Epidemiology (OSE) completed a review of all approved GBCAs and the risk of NSF. In this review, OSE evaluated drug use, postmarketing adverse event reports[c] and published literature to assess "the possibility of differences in the risk of NSF with use of GBCAs[d] (Kaiser et al. 2009)." Based upon this review, OSE reviewers concluded that GBCAs were associated with "varying risk" of NSF. They inferred that "highest risk" was associated with exposure to gadodiamide, gadopentetate dimeglumine and gadoversetamide[e] while the "lowest risk" was associated with exposure to gadoteridol and gadobenate dimeglumine.[f] The OSE reviewers deemed the published literature inadequate to determine the differential risk of the various GBCAs and NSF. Based upon this review, OSE recommended "differential labeling of GBCAs for use in certain populations

[c] FDA's Adverse Event Reporting System (AERS)
[d] This review included gadobenate dimeglumine, gadodiamide, gadopentetate dimeglumine, gadoteridol, and gadoversetamide. GBCAs approved in 2008 (gadofosveset trisodium and gadoxetate disodium) were not considered in this review.
[e] Gadodiamide, gadopentetate dimeglumine, gadoversetamide are linear GBCAs (See **Appendix A**)
[f] Gadobenate dimeglumine is a linear GBCA and gadoteridol is a macrocyclic GBCA (See **Appendix A**)

reflecting varying risk across products." OSE presented the findings from this review at the December 2009 joint advisory committee meeting, and the committees recommended contraindicating the GBCAs most commonly associated with NSF (i.e., gadodiamide, gadopentetate dimeglumine, gadoversetamide)[e] in patients with glomerular filtration rate (GFR) <30 mL/min/1.73m^2 (FDA 2009b, FDA 2017).

Relevant Product Labeling

In December 2010, FDA approved labeling supplements for all GBCAs[g] which included revisions to the BOXED WARNING for all GBCAs and CONTRAINDICATIONS for gadodiamide, gadopentetate dimeglumine, gadoversetamide as described in more detail below (Lantheus 2013, Bayer 2018, Bracco 2018, GE 2018, Liebel-Flarsheim 2018d, Guerbet 2019, Bracco 2020, Bayer 2021, Bayer 2022).

The current BOXED WARNING regarding NSF for GBCAs includes the following:

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or
  - Acute kidney injury
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing
- Do not exceed the recommended PRODUCT NAME dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration

The CONTRAINDICATIONS section for gadodiamide, gadopentetate dimeglumine, gadoversetamide includes the following:

- Chronic, severe kidney disease (glomerular filtration rate, GFR < 30 mL/min/1.73m2), or
- Acute kidney injury

[g] Gadobenate dimeglumine, gadodiamide, gadofosveset trisodium, gadopentetate dimeglumine, gadoteridol, gadoversetamide, and gadoxetate disodium

2 METHODS AND MATERIALS

2.1 CASE SELECTION AND DEFINITION

For this review, we restricted our evaluation of reports to those where the age of affected individual was clearly specified as 6 years or younger. We further defined NSF cases as reports from FAERS and medical literature that documented the following:

- GBCA exposure prior to NSF onset
- Diagnosis of NSF (e.g., histopathology supportive of NSF; pathologic findings described as NSF or suspected NSF in a report from a health care professional)

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*

Date of search	June 6, 2022
Time period of search	All reports through June 5, 2022
Search type	RxLogix PV Report
Product terms	Active moiety†: gadobenic acid, gadobutrol, gadodiamide, gadofosveset, gadolinium, gadolinium cation (3+), gadopentetate, gadopentetate dimeglumine, gadoteric acid, gadoteridol, gadoversetamide, gadoxetic acid, motexafin gadolinium
MedDRA search terms (Version 25.0)	PT- *Nephrogenic systemic fibrosis*‡
Narrative text search§	"year," "month," "week"

* See **Appendix B** for a description of the FAERS database.
† Consistent with previous DPV reviews related to GBCAs
‡ This PT encompasses LLTs *Nephrogenic systemic fibrosis and Nephrogenic fibrosing dermopathy*
§ To identify additional reports for pediatric patients that might not have been identified by filtering of the coded variable for age

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

For reports retrieved using the search parameters outlined in **Table 2**, we initially filtered by the structured data element for age associated with each FAERS report. To identify additional FAERS reports, we also performed a narrative text search on all reports retrieved using the key words outlined in **Table 2**.

2.3 LITERATURE SEARCH STRATEGY

DPV searched the medical literature with the strategy described in **Table 3**.

Table 3. Literature Search Strategy		
Date of search	June 6, 2022	June 6, 2022
Database	Embase	PubMed@FDA
Search terms	'gadolinium based contrast agent'/exp AND 'nephrogenic systemic fibrosis'/exp	(("gadolinium"[MeSH Terms] OR "gadolinium"[All Fields]) AND ("nephrogenic fibrosing dermopathy"[MeSH Terms] OR ("nephrogenic"[All Fields] AND "fibrosing"[All Fields] AND "dermopathy"[All Fields]) OR "nephrogenic fibrosing dermopathy"[All Fields] OR ("nephrogenic"[All Fields] AND "systemic"[All Fields] AND "fibrosis"[All Fields]) OR "nephrogenic systemic fibrosis"[All Fields]))
Years included in search	All	All
Other criteria	Humans	Humans, child:birth-18 years

3 RESULTS

3.1 FAERS CASES

The FAERS search described in **Table 2** retrieved 3,072 reports. Of the 2,358 reports that reported age (ranged from 8 to 93 years), we did not identify any FAERS reports describing individuals aged 6 years and younger.

3.2 LITERATURE CASES

Of the 76 articles that we retrieved using the search strategy in **Table 3**, we did not identify relevant cases.

Of note, two articles (a systematic review and a systematic search of databases) reported NSF in two 6-year-old children (Nardone et al. 2014, Attari et al. 2019). However, these cases did not provide information regarding prior use of GBCAs and therefore were not included in the case series.[h,i]

[h] Nardone et al. identified 23 pediatric patients with NSF and 17 of which had documented exposure to GBCAs (age ranged from 8 to <18 years). Of the remaining six patients who did not have documented exposure to GBCAs, one was a 6-year-old child.

4 REVIEWER COMMENTS

Our review of FAERS and the medical literature did not identify cases of NSF occurring with use of GBCAs among individuals aged 6 years and younger.

Although we did not identify cases of NSF with GBCAs used in children 6 years and younger in this review, an article by Nardone et al (Nardone et al. 2014) identified 23 pediatric patients (mean age 13.6 years, range 6 - 18 years) with NSF from FAERS, a registry known as the "International Center for NSF Research[j]" and published case reports. Of the 23 pediatric patients included in this article, 17 reported prior use of GBCAs. Commonly reported GBCAs were gadodiamide followed by gadopentetate dimeglumine, gadoteridol, gadoversetamide, and gadobenate dimeglumine/gadobenic acid. Among 13 patients with known renal disease, 10 patients were on hemodialysis or peritoneal dialysis (2 patients had acute kidney injury), 1 patient had end stage renal disease without mention of dialysis, 1 patient had chronic kidney disease, and 1 patient had renal osteodystrophy. Among 10 patients with reported outcomes, 6 died (including 2 deaths after kidney transplant[k]) and 4 reported improvements of NSF (after kidney transplant [1] or treatment[l] [1]).

Current labeling for all GBCAs contains a BOXED WARNING regarding NSF in patients with impaired renal function though does not specify risks of NSF in the pediatric population, stating only: "the adverse reactions were similar to those reported in adults" under ADVERSE REACTIONS or USE IN SPECIFIC POPULATIONS, *Pediatric Use* sections (Lantheus 2013, Bayer 2018, Bracco 2018, GE 2018, Liebel-Flarsheim 2018d, Guerbet 2019, Bracco 2020, Bayer 2021, Bayer 2022).

We note important limitations of this analysis. We underscore the universal problems of spontaneous reporting databases such as FAERS, including but not limited to underreporting, as well as limited and variable quality of information in spontaneous reports. In addition, underreporting may be influenced by whether the event is labeled and how long the drug has been on the market. NSF is a known adverse event associated with GBCA use and GBCAs have been available for a long time; therefore, consumers and healthcare providers are less likely to report (La Grenade et al. 2001, McAdams et al. 2008). Medicolegal pressures may prevent healthcare institutions from publishing cases related to NSF potentially resulting in underreporting of cases in the literature as well. In this review specifically, inadequate reporting

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[i] Attari et al. identified 639 patients with NSF from 173 studies and 539 patients had documented exposure to GBCAs. The youngest age with reported NSF was 6 years, however, this article did not provide any further information (e.g., previous GBCA exposure).

[j] International Center for NSF Research makes the diagnosis of NSF based upon the clinical and pathological definition by Girardi et al. (Girardi et al. 2011), and the definition of NSF does not require exposure to a GBCA.

[k] One case reported initial improvement in skin lesions after kidney transplant. However, the patient experienced transplant rejection and died.

[l] One case reported "near-complete resolution after treatment with triamcinolone 0.1% and calcipotriene 0.005% with compression stockings/nocturnal leg elevation. Additional [sic] benefit with 3 days of pulsed IV methylprednisolone 750mg followed by weekly methotrexate."

regarding age could have also contributed to our inability to identify cases among individuals aged 6 years and younger.

Although we do not have specific recommendations resulting from this review, DPV will continue to monitor for postmarket reports of NSF in the pediatric population.

Addendum:
On July 21, 2022—DIRM Requested a meeting with DPV and the Division of Pediatric and Maternal Health (DPMH) to discuss whether or not existing GBCAs labeling accurately reflected the risk of NSF in the pediatric population. DPMH described a theoretical concern regarding the risk of NSF for pediatric patients with immature kidneys (i.e., patients less than 2 years). However, based upon data provided within this review together with their independent assessment, DPMH reviewed the current gadodiamide labeling (as a representative label for the GBCAs) and concluded that current labels described risk of NSF adequately. DIRM, DPV and DPMH agreed that no labeling updates are needed at this time. However, DIRM and DPMH requested that DPV monitor for any new reports of NSF, particularly for patients younger than 2 years of age, even though this is technically an already labeled event.

5 REFERENCES

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6 APPENDICES

6.1 APPENDIX A. PRODUCT NAMES, NDA/ANDA NUMBERS, DATES OF APPROVALS, INDICATIONS, AND APPLICANTS OF GBCAS

Application Number (approval date)	Product name	Indications	Applicant	Reference to GBCAs Labeling
Linear GBCAs				
NDA-021711* (12/22/2008)	Ablavar (gadofosveset trisodium)	• MRA to evaluate aortoiliac occlusive disease in adults with known or suspected peripheral vascular disease	Lantheus Medical Imaging, Inc	(Lantheus 2013)
NDA-022090 (7/3/2008)	Eovist (gadoxetate disodium)	• MRI of the liver to detect and characterize lesions in patients with known or suspected focal liver disease	Bayer Healthcare Pharmaceuticals, Inc	(Bayer 2021)
NDA-019596† (6/2/1988) **NDA-021037†** (3/10/2000)	Magnevist (gadopentetate dimeglumine)	• MRI in adults and pediatric (2 years and older) to facilitate the visualization of lesions and abnormal vascularity in: o CNS: brain, spine and associated tissues o extracranial/extraspinal tissues: head and neck o body	Bayer Healthcare Pharmaceuticals, Inc	(Bayer 2018)
NDA-021357 (11/23/2004) **NDA-021358** (11/23/2004)	MultiHance (gadobenate dimeglumine)	• MRI of the CNS in adults and pediatric patients (including term neonates), to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine, and associated tissues • MRA of renal and aorto-ilio-femoral vessels to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease	Bracco Diagnostics, Inc	(Bracco 2018)
NDA-020123 (1/8/1993) **NDA-022066** (9/5/2007)	Omniscan (gadodiamide)	• MRI of o CNS: to visualize lesions with abnormal vascularity (or those thought to cause abnormalities in the blood-brain barrier) in the brain (intracranial lesions), spine, and	General Electric Healthcare, Inc.	(GE 2018)

Application Number (approval date)	Product name	Indications	Applicant	Reference to GBCAs Labeling
		associated tissues ○ body (intrathoracic noncardiac, intra-abdominal, pelvic and retroperitoneal regions)		
NDA 020937‡ **NDA 020975‡** **NDA 020976‡** (all 12/8/1999)	Optimark (gadoversetamide)	• MRI of ○ CNS: in patients with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues ○ Liver: to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver of patients who are highly suspect for liver structural abnormalities on computed tomography	Liebel-Flarsheim Company LLC	(Liebel-Flarsheim 2018d)
Macrocyclic GBCAs				
NDA 204781 (3/20/2013)	Dotarem (gadoterate meglumine)	• 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 and/or abnormal vascularity	Guerbet LLC	(Guerbet 2019)
ANDA 210016 (11/01/2019)	Clariscan (gadoterate meglumine)	• Same as Dotarem	General Electric Healthcare, Inc	
ANDA 215304 (4/11/2022)	Gadoterate meglumine	• Same as Dotarem	Iangsu Hengrui Med	
NDA 201277 (3/14/2011)	Gadavist (gadobutrol)	• MRI of ○ CNS: to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the CNS in adults and pediatric (including term neonates) ○ Breast in adult patients: to assess the presence and extent of malignant breast disease in adult	Bayer Healthcare Pharmaceuticals, Inc	(Bayer 2022)

Application Number (approval date)	Product name	Indications	Applicant	Reference to GBCAs Labeling
		patients ○ Cardiac: to assess myocardial perfusion (stress, rest) and late gadolinium enhancement in adult patients with known or suspected coronary artery disease • MRA to evaluate known or suspected supra-aortic or renal artery disease in adult and pediatric patients, including term neonates.		
NDA-020131 (11/16/1992) **NDA-021489** (10/9/2003)	ProHance (gadoteridol)	• MRI of ○ CNS: to visualize lesions with disrupted blood brain barrier and/or abnormal vascularity in the brain (intracranial lesions), spine and associated tissues in adults and pediatric (including term neonates) ○ extracranial/extraspinal head and neck in adults	Bracco Diagnostics, Inc	(Bracco 2020)

*On September 1, 2016, the Applicant requested withdrawal of NDA 021711 due to business reasons which are not related to the safety or effectiveness of the product. Published in the Federal Register on February 22, 2018. Approval of the application was withdrawn as of March 26, 2018 (83FR7738 February 22, 2018).

† On January 30, 2019, the Applicant requested withdrawal of NDA 019596 and 021037 due to the diminishing market demand and not related to the safety or effectiveness reasons. Published in the Federal Register on September 9, 2019. Approval of the applications was withdrawn as of October 9, 2019 (84FR47309 September 9, 2019).

‡ On August 30, 2018, the Applicant requested withdrawal of NDA 020937, 020975, 020976 due to a business decision. Published in the Federal Register on September 9, 2019. Approval of the applications was withdrawn as of October 9, 2019 (84FR47309 September 9, 2019).

Abbreviations: CNS=Central Nervous System; GBCA=gadolinium-based contrast agents; MRA= magnetic resonance angiography; MRI= magnetic resonance imaging

6.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

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

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.

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

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

Memorandum

Date: 7/22/22

To: Sharon Thomas, Regulatory Project Manager
Division of Imaging and Radiation Medicine (DIRM)

Younsook Kim, Associate Director for Labeling, DIRM

From: James Dvorsky, Team Leader
Office of Prescription Drug Promotion (OPDP)

For: Nazia Fatima, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for GADOPICLENOL INJECTION for intravenous use

NDA: 216986

In response to DIRM consult request dated March 7, 2022, OPDP has reviewed the proposed product labeling (PI) and Medication Guide (MG) for the original NDA submission for GADOPICLENOL INJECTION for intravenous use (gadopiclenol).

OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DIRM on July 18, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on July 22, 2022.

Thank you for your consult. If you have any questions, please contact James Dvorsky (james.dvorsky@fda.hhs.gov) or Nazia Fatima 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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/s/

JAMES S DVORSKY on behalf of NAZIA FATIMA
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for Nazia Fatima

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 22, 2022
To:	Sharon Thomas Regulatory Project Manager **Division of Imaging and Radiation Medicine (DIRM)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	GADOPICLENOL injection
Dosage Form and Route:	for intravenous use
Application Type/Number:	NDA 216986
Applicant:	Guerbet, LLC

1 INTRODUCTION

On January 21, 2022, Guerbet, LLC submitted for the Agency's review an original New Drug Application (NDA) 216986 for GADOPICLENOL injection, for intravenous use, a New Molecular Entity (NME). The proposed indication for GADOPICLENOL injection is for use in adults and children aged 2 years and older in magnetic resonance imaging (MRI) (b) (4) lesions in the Central Nervous System (brain, spine, and (b) (4) tissues), and the Body (head and neck, thorax (b) (4), abdomen (b) (4), pelvis (b) (4), and musculoskeletal system).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Imaging and Radiation Medicine (DIRM) on July 8, 2022 and March 3, 2022 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for GADOPICLENOL injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft GADOPICLENOL injection MG received on January 21, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 8, 2022.
- Draft GADPICLENOL injection Prescribing Information (PI) received on January 21, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 8, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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JAMES S DVORSKY
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for Nazia Fatima

NYEDRA W BOOKER
07/22/2022 11:43:33 AM

SHARON W WILLIAMS
07/22/2022 11:52:54 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	5/31/2022		
To:	Sharon Thomas		
Requesting Center/Office	CDER	**Clinical Review Division**	Choose an item.
From	Elvira Castro OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans Injection Devices Team Leader OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	Case# 00820546 ICC: 2200157 Submission: IND 216986 Sponsor : Guerbet, LLC Drug/Biologic; Gadopiclenol Indications for Use: Indicated		
Recommendation	**Final Recommendation:** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies		
	Comments to Review Team: No additional comment		
	PMC/PMR or CR Deficiencies: **No CR deficiencies.**		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Elvira E. Castro -S Digitally signed by Elvira E. Castro -S Date: 2022.05.31 07:48:38 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2022.06.02 21:40:44 -04'00'	

1. PURPOSE

The purpose of this consult is to review the type 2 drug/device combination product (PFS drug delivery system) because the sponsor is adding PFS in plastic container. The syringe presentation has 3 different filled volume (7.5, 10, 15mL). The drug is Gadopiclenol dosage of 0.1mL/Kg body weight It is given intravenously.

This review will cover the following review areas:

☒ Device performance
☒ Stability – device performance on stability
☒ Essential Performance Requirements (EPR) Control strategy

☒ **CDRH Quality Systems Assessment / Facilities consult not required**

It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential[1]) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

The syringe presentation of Gadopiclenol 0.5 mmo/mL is packaged in a (b) (4) plastic syringe with elastomer plunger stopper and capped with an elastometric tip

The pre-filled syringe presentations are:

- 15-mL syringe filled to 7.5 mL
- 15-mL syringe filled to 10mL
- 15-mL syringe filled to 15 ml

All the components of the plastic prefilled syringes (PFS) used for Gadopiclenol 0.5 mmol/mL comply with the corresponding current USP chapters:

- Barrel: USP <661> "Containers – Plastics",
- Plunger stopper and tip cap: USP <381> "Elastomeric Closures for Injection"
- All: USP <87> "Biological Reactivity Tests, in vitro" and <88> "Biological Reactivity Test, in vivo"

SPECIFICATIONS

1. Syringe Barrel- tested for appearance, identification, dimensional evaluation and bacterial endotoxins

Table 1: Specifications for 15 mL (b) (4) Syringe Barrel - (b) (4)

Test	Acceptance Criteria	Analytical Procedures
Appearance	Clean, uniform size, shape and color	Visual inspection
Identification	To pass test	Infrared spectrophotometry
Dimensional Evaluation	Conforms to drawing	Physical measurements
Bacterial Endotoxins	NMT (b) (4)	EP 2.6.14 or USP <85>

2. Plunger Stopper

Table 2: Specifications for (b) (4) Plunger Stopper- (b) (4)

Test	Acceptance Criteria	Analytical Procedures
Appearance	Clean, uniform size, shape and color	Visual inspection
Identification	To pass test	Infrared spectrophotometry
Bacterial Endotoxins	NMT (b) (4)	EP 2.6.14 or USP <85>

3. Tip Cap

Table 3: Specifications for (b) (4) Tip Cap - (b) (4)

Test	Acceptance Criteria	Analytical Procedures
Appearance	Clean, uniform size, shape and color	Visual inspection
Identification	To pass test	Infrared spectrophotometry
Bacterial Endotoxins	NMT (b) (4)	EP 2.6.14 or USP <85>

[1] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

2.1. Picture of Final Device Presentation

No final presentation included in the submission.

2.2. Design Requirements

Syringe Description

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Professional user
Injection Site	Intravenous use only
Injection tissue and depth of injection	n/a
Needle connection (e.g. luer, slip tip, staked)	Luer lock
Syringe Volume	15mL
Delivered Dose Volume	0.5 mmol/mL based on the patient individually based on the body weight.

Additional Devices

Requirement	Describe
Hypodermic Needle: (length, gauge)	n/a
Safety Features (e.g. Needle safety component/device)	n/a

3. DEVICE PERFORMANCE REVIEW

Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Stability Module 3.2.P.8 (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	In 3mL syringe	Y	Y	Y	

	= (b) (4) 9mL syringe = (b) (4)				
Break loose Force	(b) (4)	Y	Y	Y	
Glide Force	(b) (4)	Y	Y	Y	
Cap Removal Force	(b) (4) N	Y	Y	n/a	n/a

Reviewer Comments

PFS aspect is followed in stability studies, at time point 0, after 6 months under accelerated conditions at 40 ± 2°C / NMT 25 % RH and after 12, 24 and 36 months under long-term stability conditions at 25 ± 2°C /40 % RH.

- According to the stability study of the deliverable Volume, the volume will be delivered using the label placed in the PFS. So, the test was performed to demonstrate the adequacy of the label's graduation regarding the precision of the delivered volume needed by the clinical practice. The deliverable volume was tested using 3mL syringe to deliver 3mL and 9mL syringe to deliver 9mL.

Table 11: Deliverable Volume Results

		Deliverable volume (mL)	
		PFS 7.5 mL/15mL	PFS 15 mL/15mL
Target tested		3 mL	9 mL
T0	Deliverable volume minimum	2.8	8.7
	Deliverable volume maximum	3.0	
T6M 40°C±2°C/NMT 25% RH	Deliverable volume minimum	2.9	8.7
	Deliverable volume maximum	3.0	
T12M 25°C±2°C/40% RH ± 5% RH	Deliverable volume minimum	2.8	8.9
	Deliverable volume maximum	3.0	

Table 9: Plunger Release Force Results (kg)

Batch Number	Presentation	T0	T6 Months 40°C/NMT 25% RH	T12 Months 25°C/40% RH
19M025-A1$^{\alpha}$	PFS 7.5/15 mL	2.4 to 3.0	5.4 to 5.9	NP
19M025-A2$^{\beta}$		2.2 to 2.8	NP	1.7 to 2.5
19M026-A1$^{\alpha}$		2.4 to 2.6	4.7 to 6.3	NP
19M026-A2$^{\beta}$		2.4 to 2.8	NP	1.6 to 2.8
19M027-A1$^{\alpha}$		2.6 to 2.7	4.9 to 5.6	NP
19M027-A2$^{\beta}$		2.4 to 2.8	NP	1.8 to 2.5
19M025-B1$^{\alpha}$	PFS 15/15 mL	2.6 to 3.9	5.6 to 6.6	NP
19M025-B2$^{\beta}$		2.5 to 3.2	NP	2.6 to 3.6
19M026-B1$^{\alpha}$		2.9 to 3.3	5.6 to 6.5	NP
19M026-B2$^{\beta}$		2.9 to 3.5	NP	2.5 to 3.3
19M027-B1$^{\beta}$		3.2 to 3.5	NP	2.5 to 3.7
19M027-B2$^{\alpha}$		3.1 to 3.3	5.5 to 6.5	NP

Table 10: Plunger Travel Force Results (kg)

Batch Number	Presentation	T0	T6 Months 40°C/ NMT 25% RH	T12 Months 25°C/40% RH
19M025-A1$^{\alpha}$	PFS 7.5/15 mL	1.1 to 1.3	1.1 to 1.2	NP
19M025-A2$^{\beta}$		1.0 to 1.2	NP	0.7 to 0.8
19M026-A1$^{\alpha}$		1.1 to 1.3	1.0 to 1.2	NP
19M026-A2$^{\beta}$		1.1 to 1.2	NP	0.7
19M027-A1$^{\alpha}$		1.1 to 1.3	1.1 to 1.3	NP
19M027-A2$^{\beta}$		1.1 to 1.4	NP	0.7 to 0.8
19M025-B1$^{\alpha}$	PFS 15/15 mL	1.3 to 1.5	1.4	NP
19M025-B2$^{\beta}$		1.3 to 1.6	NP	1.2 to 1.3
19M026-B1$^{\alpha}$		1.5 to 1.8	1.3 to 1.7	NP
19M026-B2$^{\beta}$		1.4 to 1.7	NP	1.2 to 1.4
19M027-B1$^{\alpha}$		1.5 to 1.7	NP	1.4 to 1.6
19M027-B2$^{\beta}$		1.6	1.1 to 2.1	NP

Conclusion: The result that the sponsor provided is consistent to the intended use of the device/drug combination. Based on the report the device aspect is not impacted by the drug nor the storage. However, as it was mentioned in the discussion yesterday, the sponsor provided the summary report of the essential performance of their device. It is not clear whether the stability of the PFS break loose and gliding force was performed. An IR was sent to the sponsor

5/16/2022 to verify whether the stability of the PFS BL/GF was performed. If it was done to provide the location. The sponsor provided the location in 3.2.P.2.4 Container Closure System -PFS with the following justification that the result shows a stability of the mechanical properties of the syringe during stability period result. No impact of the drug product on the parameter of the drug product on the parameters of the syringes. The sponsor also stated that according to ICH Q6A the development results justify that the mechanical properties don't need to be routinely tested. The acceptance criteria of all the testing were included for the PFS All LOA and Quality analysis were included. What the sponsor provided was adequate.

4. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	In-process and or release testing	Y
Break loose Force		NA
Glide Force		NA

Reviewer Comments

For the development of the GAdopiclenol, Guerbet follows a combination of traditional and an enhanced pharmaceutical development approach. The risk management and the scientific knowledge were used to identify and understand process parameters and unit operations that impact the critical quality attributes (CQAs) of the drug substance and develop appropriate control strategies of the drug substance (either by a process parameter, or by a testing). This approach has not been followed until the establishment of design space(s). Therefore, the process reproducibility has been demonstrated by a traditional approach, that means with the manufacture of three batches at the same set points and the same operating range for process parameters and testing, in order to meet established acceptance criteria.

<<END OF REVIEW>>

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SHARON P THOMAS
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Clinical Inspection Summary

Date	July 12, 2022
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D., Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE)
To	Sharon Thomas, Regulatory Project Manager Hadi Bagheri, M.D., Medical Officer Shane Masters, M.D., Clinical Team Leader Libero Marzella, M.D., Ph.D., Division Director Division of Imaging and Radiation Medicine (DIRM)
Application	NDA 216986
Applicant	Guerbet LLC, USA
Drug	Gadopiclenol (b) (4)
Original NDA	Yes (New Molecular Entity)
Review Timeframe	Priority
Proposed Indication	MRI enhancement in evaluating lesions in the CNS and other body sites
Consultation Date	March 24, 2022
CIS Goal Date	July 21, 2022
Action Goal Date	September 21, 2022 (or earlier TBD)
PDUFA Due Date	September 21, 2022

I. OVERALL ASSESSMENT OF FINDINGS

Studies GDX-44-010 and GDX-44-011 were audited at good clinical practice (**GCP**) inspections of four study sites: three clinical investigators (**CI**), Drs. Roberts, Otto and Gaballah, selected as the major representative sites to audit general study conduct and adverse event (**AE**) data, and an imaging contract research organization (**CRO**), (b) (4) (b) (4) to verify the primary efficacy (imaging) endpoint data. No significant GCP findings were identified at the four study sites; both GDX-44-010 and GDX-44-011 appear to have been conducted in adequate compliance with GCP standards and FDA regulations. The clinical data generated at the four inspected study sites appear to be acceptable in support of the sponsor's proposed product indication for use.

II. BACKGROUND

This original New Drug Application (**NDA**) for gadopiclenol (b) (4) is based on 8 major clinical studies, of which two Phase 3 studies (GDX-44-010 and GDX-44-011) were audited on-site at GCP inspections of three CIs and one CRO. The four sites were selected for inspection based on preliminary NDA data analyses of world-wide regional data (imaging efficacy and safety), which supported the four sites as an adequate sample of over 60 sites that participated in the two studies. For either study, (b) (4) was the only CRO that participated in image interpretation (primary efficacy data). The oversight of study conduct at (b) (4) was performed directly by the sponsor. The proposed clinical indication for (b) (4) (provisional trade name) is:

*For intravenous (**IV**) use in adults and children (age ≥ 2 years) in magnetic resonance imaging (**MRI**)* (b) (4) *lesions in the central nervous system (**CNS**) and in the body (head and neck, thorax, abdomen, pelvis, and musculo-skeletal)*

GDX-44-010: *Efficacy and Safety of Gadopiclenol for Central Nervous System Magnetic Resonance Imaging* (PICTURE)

This double-blinded cross-over study was conducted over 15 months (6/2019 – 9/2020) in 256 adults randomized at 33 CI sites world-wide: United States (**US**, 8 sites), Hungary (5), France (4), Italy (4), Spain (3), Belgium (2), Mexico (2), South Korea (2), Germany (1), Poland (1), and Taiwan (1). The primary study objective was to demonstrate the superiority of gadopiclenol-enhanced CNS MRI (0.05 mmol/kg) relative to unenhanced CNS MRI for the imaging elements of (co-primary endpoints): border delineation, internal morphology, and degree of contrast enhancement (**CE**). The study was pair-controlled in two ways: (1) before versus after gadopiclenol CE; and (2) gadopiclenol CE versus gadobutrol CE (active control). The study consisted of 5 visits:

- V1: screening, up to 7 days prior to randomization
- V2: randomization, unenhanced MRI, and first contrast-enhanced MRI (**CE-MRI**)
- V3: safety visit on the day after V2
- V4: second CE-MRI, 2-14 days after V2
- V5: safety visit on the day after V4

Adult subjects with one or more known (or highly suspected) CNS lesions were enrolled if previous imaging (within 12 months) showed disrupted blood brain barrier (**BBB**). Multiple MRIs were obtained for each subject: before and after CE, and with gadopiclenol and gadobutrol (Visits 2 and 4, randomly assigned). A single designated unblinded study personnel administered the two study medications: (1) gadopiclenol, single IV bolus injection, 0.05 mmol/kg; and (2) gadobutrol, single IV bolus injection, 0.10 mmol/kg.

At each CI site, one or more radiologists interpreted the MRI images on-site (secondary endpoint). Additionally, the images were interpreted centrally at (b) (4) by 4 independent radiologists (3 primary, 1 adjudicator) using electronic Case Report Forms (**eCRFs**).

- ***Primary efficacy endpoint:*** lesion visualization (border delineation, internal morphology, and CE degree) for gadopiclenol (pre-CE versus post-CE) as assessed by independent central readers at (b) (4)

- ***Major secondary efficacy endpoint:*** lesion visualization (same as for primary efficacy endpoint) for gadopiclenol CE relative to gadobutrol CE

Mean lesion scores were calculated for quantitative endpoint assessment using a 4-point scale: sum of scores for multiple lesions divided by the number of lesions, for up to 3 matching lesions. The sponsor claims statistically significant demonstration of gadopiclenol efficacy without significant AEs: (1) superior lesion visualization, gadopiclenol CE-MRI relative to unenhanced MRI; and (2) non-inferior lesion visualization, gadopiclenol CE (0.05 mmol/kg) relative to gadobutrol CE (0.10 mmol/kg).

GDX-44-011: *Efficacy and Safety of Gadopiclenol for Body Magnetic Resonance Imaging* (PROMISE)

This study was conducted over 16 months (8/2019 – 12/2020) in 304 adults randomized at 33 CI sites world-wide: US (7 sites), Poland (5), South Korea (5), Germany (4), France (3), Hungary (2), Mexico (2), Ukraine (2), Bulgaria (1), Italy (1), and Spain (1). Adult subjects with one or more known (or highly suspected) enhancing lesions (previous imaging within 12 months) in the following body regions were enrolled: head and neck, thorax, abdomen, pelvis, and musculoskeletal system. The study was otherwise nearly identical to GDX-44-010 (study objective, design, and execution), as were the sponsor conclusions about gadopiclenol safety and efficacy as an MRI contrast agent.

III. INSPECTION RESULTS

1. Donna R. Roberts, M.D.

Medical University of South Carolina
96 Jonathan Lucas Street
MSC 323, Suite 210 CSB
Charleston, South Carolina 29425

Inspection dates: May 10-11, 2022

GDX-44-010, Site 84002: 8 subjects were screened, 8 were enrolled, and 7 completed the study (1 withdrew). Subject case records were reviewed in detail for all subjects.

The observed deficiencies were limited to a few scattered instances of incomplete or inaccurate information on source records (study data, MRI scores) or on administrative records (e.g., study task delegation log), which appeared to be isolated recordkeeping errors. The correct information was consistently captured elsewhere, on corresponding administrative records or on source (paper) and electronic CRFs. Study data were accurately reported in the NDA.

The deficiency observations appear unlikely to be significant. GCP deficiencies were otherwise not observed. Study monitoring (by (b) (4)) and oversight by the local institutional review board (**IRB**) appeared to be adequate. Study files and subject case records were well maintained and readily available for review. No unreported protocol deviations were discovered. All audited major efficacy endpoint data (applicable to CI site) were verifiable against the data reported in the NDA.

2. Pamela M. Otto, M.D.

University of Texas Health Science Center
903 West Martin Street, MS-36-2
San Antonio, Texas 78207

Inspection dates: May 16-18, 2022

GDX-44-011, Site 84005: 25 subjects screened, 25 were enrolled, and 23 completed the study (2 withdrew). Subject case records were reviewed in detail for all subjects.

No significant GCP deficiencies were observed, including no unreported AEs or protocol deviations. Study monitoring and IRB oversight appeared to be adequate. Study files and subject case records were well maintained. All audited efficacy endpoint data (applicable to CI site) were verifiable against the data reported in the NDA.

3. Ayman H. Gaballah, M.D.

University of Missouri Hospital and Clinic
One Hospital Drive
Columbia, Missouri 65212

Inspection dates: June 7-10, 2022

GDX-44-010, Site 84009: 9 subjects were screened, 9 were enrolled, and 9 completed the study. Subject case records were reviewed in detail for all subjects.

No significant GCP deficiencies were observed, including no unreported AEs or protocol deviations. Study monitoring and IRB oversight appeared to be adequate. Study files and subject case records were adequately maintained. All audited efficacy endpoint data (applicable to CI site) were verifiable against the data reported in the NDA.

Note: The Establishment Inspection Report (**EIR**) has not been received from the field office as of this Clinical Inspection Summary (**CIS**) communication. The inspectional findings noted above are based on preliminary communication with the field investigator. If new significant findings are discovered upon receipt and completion of EIR review, an addendum to this CIS will be forwarded to the review division.

4. (b) (4)

(b) (4)

Inspection dates: (b) (4)

GDX-44-010 and GDX-44-011: The role of this CRO in the two studies was limited to the independent interpretation of the MRI images obtained at CI sites to support the determination and analyses of the efficacy data (diagnostic utility of gadopiclenol).

The inspection consisted of a detailed on-site review of: (1) study protocols; (2) contractual agreement and communication with the sponsor; (3) staff qualification and training records; (4) general and special standard operating procedure (**SOP**) manuals,

including the MRI imaging charter (*Read Completion Guidelines*) and the MRI quality control manual (*Acquisition of MRI Scans Guidelines*); (5) validation and certification of electronic data systems; and (6) primary written source imaging data, in parallel with review (demonstration) of the MRI images.

- A total of 560 subjects were enrolled in the two studies combined. Subject records and MRI images were reviewed for the 42 subjects enrolled at the three inspected CI sites.
- The MRI images from CI sites were submitted to (b) (4) through *SMART*, an electronic image transfer system, then transferred to *Study Direct*, another electronic system for image processing, quality control, and presentation for interpretation.
- The study data were sent to the sponsor every 6 weeks (*Secure File Transfer Program*) in accordance with the procedures specified in the accompanying SOP manual.
- All data systems used to support the two studies were non-commercial electronic systems, built and validated internally by the CRO (compliant with 21 CFR Part 11).

No significant GCP deficiencies were observed. Study files and subject case records were well maintained. No unreported protocol deviations were discovered. The audited primary endpoint data were verifiable against the data reported in the NDA.

{See appended electronic signature page}

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Central Document Room / NDA 216986

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/s/

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Division of Pediatrics and Maternal Health Review

Date: May 22, 2022 **Date consulted:** March 22, 2022

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM), Office of New Drugs (OND)

Through: Miriam, Dinatale, D.O., Team Leader, DPMH, ORPURM, OND

Lynne P. Yao, MD, OND, Division Director, DPMH, ORPURM, OND

To: The Division of Imaging and Radiation Medicine (DIRM)

Drug: GADOPICLENOL Injection

NDA: 216986

Applicant: Guerbet LLC

Subject: Pregnancy and Lactation Labeling Recommendations and Formatting

Indication: For adults and children aged 2 years and older for contrast enhanced Magnetic Resonance Imaging (MRI) (b) (4) lesions in:

- The Central Nervous System (brain, spine and (b) (4) tissues),
- The Body (head and neck, thorax (b) (4), abdomen (b) (4), pelvis (b) (4), and musculoskeletal system)

Materials Reviewed:

- January 21, 2022, New Drug Application (NDA) 216986 submission for Gadopiclenol Injection
- March 22, 2022, DIRM consult for DPMH to review and provide PLLR recommendations and formatting, DARRTS reference ID 4956724
- November 7, 2019, DPMH literature and labeling review for multiple gadolinium imaging products, Omniscan (NDAs 20123, 22066), Magnevist (NDA 19596), Gadavist (NDA 201277), Eovist (22090), ProHance (NDAs 20131, 21489), MultiHance (NDAs 21357, 21358), Ablavar (NDA 21711), Optimark (NDAs 20937, 20975, 20976), Dotarem (204781); Erica Radden, MD, Medical Officer, DARRTS Reference ID 4514372[1]

Consult Question: "DIRM kindly request participation in the team and labeling meetings."

INTRODUCTION

On January 21, 2022, Guerbet LLC submitted an original New Drug Application (NDA 216986) for Gadopiclenol injection for adults and children aged 2 years and older for contrast enhanced Magnetic Resonance Imaging (MRI) (b) (4) lesions in:

- The Central Nervous System (brain, spine and (b) (4) tissues),
- The Body (head and neck, thorax (b) (4), abdomen (b) (4), pelvis (b) (4), and musculoskeletal system).

The Division of Imaging and Radiation Medicine (DIRM) consulted the Division of Pediatric and Maternal Health (DPMH) on March 22, 2022, to assist with the Pregnancy and Lactation subsections of labeling.

BACKGROUND

- Gadopiclenol is a macrocyclic gadolinium (Gd)-based contrast agent (GBCA) intended to be used by intravenous (IV) injection as a contrast agent for magnetic resonance imaging (MRI).[2,3]
- GBCAs are used for detecting and delineating lesions and associated tissues. GBCA's are classified as linear or macrocyclic agents based on their chemical structure. Multiple publications demonstrate that linear GBCAs have a higher association with brain deposition than macrocyclic GBCAs.
- Refer to Appendix A for the applicant's proposed labeling language.

[1] The referenced review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below. Although there is overlap in the labeling proposed for the current product and labeling that appears in approved product labeling, the labeling recommendations in this review are based on DPMH's independent analysis of the underlying data.

[2] ACR Committee on Drugs and Contrast Media. ACR manual on contrast media, version 10.3 (2020). https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 5, 2022.

[3] European Society of Urogenital Radiology. ESUR guidelines on contrast agents, version 10.0 (2018). https://www.esur.org/fileadmin/content/2019/ESUR_Guidelines_ 10.0_Final_Version.pdf. Accessed May 5, 2022.

- DIRM issued two drug safety communications (DSCs) on GBCAs and the risk of gadolinium retention in the brain, bone and skin in July 2015[4] and May 2017[5]. These drug safety communications were issued based on the concern regarding gadolinium retention in patients' bodies, including the brain for months to years after receiving the drugs. However, to date no evidence of adverse events, other than nephrogenic systemic fibrosis which is listed in a boxed warning in each labeling, associated with GBCA retention has been identified.[6]
- July 27, 2018, DIRM submitted a supplement request letter to GBCAs in PLR format requesting the following statement summarizing the information in Section 8.1 of the Prescribing Information be added to the highlights:

  ----------USE IN SPECIFIC POPULATIONS----------
  Pregnancy: Use only if imaging is essential during pregnancy and cannot be delayed. (8.1)
- Additionally, in the July 27, 2018 supplement request letter, the Agency included an outline of postmarketing study requirements including animal studies in mice and juvenile non-human primates to further evaluate the effects of gadolinium retention on fetal and neonatal development and a clinical trial comparing neurologically normal adults to matched controls to evaluate the effects of repetitive administration of the respective GBCAs on neurologic and systemic function using a comprehensive battery of neurobehavioral testing and other clinical and laboratory tests over the course of at least five administrations. Within 30 days of the date of the letter, each application holder was required to submit a proposal to the Agency to address these requirements including proposed timelines. Application holders were encouraged to collaborate with other application holders of GBCA products on the conduct of these postmarketing requirements because a uniform protocol and methodology standard (e.g. dose, dose multiples, dose timing, dose frequency, observational batteries and timing of evaluations) encompassing all the GBCAs would provide the most useful generalizable data. Furthermore, class-wide Safety Labeling Change requirements were also issued. The Agency approved updated language for all marketed GBCAs, which included the recommended safety labeling changes related to pregnancy.
- On November 7, 2019, DPMH completed a review of multiple gadolinium imagining products and their use during pregnancy.[7] At the time, DPMH provided labeling recommendations for pregnancy sections of all GBCA labeling based on a review of literature and professional guidelines. Refer to Appendix B for a summary of past DPMH reviews on gadolinium products and exposure during pregnancy.
  - According to previous DPMH reviews, GBCAs cross the human placenta and may result in fetal exposure and retention of gadolinium. In addition, cohort and case reports reviewed on exposure to GBCAs during pregnancy have not reported a clear association between GBCAs and adverse effects in the exposed neonate;

[4] http://www.fda.gov/Drugs/DrugSafety/ucm455386.htm
[5] https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm
[6] https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-identifies-no-harmful-effects-date-brain-retention-gadolinium
[7] November 7, 2019, DPMH literature and labeling review for multiple gadolinium imaging products, Omniscan (NDAs 20123, 22066), Magnevist (NDA 19596), Gadavist (NDA 201277), Eovist (22090), ProHance (NDAs 20131, 21489), MultiHance (NDAs 21357, 21358), Ablavar (NDA 21711), Optimark (NDAs 20937, 20975, 20976), Dotarem (204781); Erica Radden, MD, Medical Officer, DARRTS Reference ID 4514372.

however, a retrospective cohort study comparing pregnant women who had a GBCA MRI to those who did not have an MRI reported a higher incidence of stillbirths and neonatal deaths; however, these data are limited by lack of comparison with non-contrast MRI and lack of information about the indication for MRI.
    - Additionally, the labeling language in subsection 8.1 Pregnancy of gadolinium imagining products recommends that because of the potential of gadolinium risk to the fetus, that these products are only used if imaging is essential during pregnancy and cannot be delayed.
- In 2019, the FDA along with Harvard Medical School and Harvard Pilgrim Health Care conducted a retrospective study using the Sentinel database to identify pregnancies in the United States that resulted in live-births from 2006 through 2017 that were exposed to gadolinium-based contrast agents for MRI.[8] The majority of MRI exams were performed for the head, pelvic area and abdominal area. The study showed higher rates of GBCA exposure during the first few weeks of pregnancy compared with later in pregnancy. The authors suggest that many of these exposures may have occurred before the pregnancy was recognized.[8]

[8] Bird S, K Gelperin, L Sahin, K Bleich, E Fazio-Eynullayeva, C Woods, et al. First-Trimester Exposure to Gadolinium-based Contrast Agents: A Utilization Study of 4.6 Million U.S. Pregnancies. Radiology 2019;293:193-200.

Drug Characteristics and Labeling Information[9]

Drug Classification	Contrast enhanced MRI
Mechanism of Action	The contrast enhancing effect is mediated by gadopiclenol, which is a macrocyclic non-ionic complex of gadolinium. This active moiety enhances the relaxation of water protons in its vicinity in the body and increases signal intensity (brightness) of tissues.
Dose and Administration	0.1 mL/kg body weight (equivalent to 0.05 mmol/kg) in adults and pediatric patients 2 years and older Each mL contains 485.1 mg of gadopiclenol as active ingredient which is equivalent to 0.5 mmol and 78.6 mg of gadolinium
Molecular Weight	970.11 g/mol
Protein Binding	none
Mean Plasma Elimination Half-Life	1.5 and 1.7 hours
Warnings and Precautions	Increased risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. GBCA risk of NSF is highest among patients with chronic, severe kidney disease. Acute kidney injury Gadolinium retention (b) (4)
Adverse Reactions (b) (4)	Injection site pain, headache, nausea, injection site coldness, fatigue, diarrhea, abdominal pain, injection site edema, dysgeusia, injection site warmth, feeling hot.

[9] January 21, 2022, New Drug Application (NDA) 216986 submission for Gadopiclenol Injection.

REVIEW

PREGNANCY

Imaging Studies and Overall Radiation Exposure during Pregnancy

The American College of Obstetrics and Gynecology (ACOG) [10] Guidelines, updated in 2017, explain that imaging studies to evaluate acute and chronic conditions are sometimes necessary during pregnancy. Additionally, ACOG states the following:

- "Ultrasonography and magnetic resonance imaging (MRI) are not associated with risk and are the imaging techniques of choice for the pregnant patient, but they should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient.
- With few exceptions, radiation exposure through radiography, computer tomography (CT) scan, or nuclear medicine imagine techniques is at a dose much lower than the exposure associated with fetal harm. If these techniques are necessary in addition to ultrasonography or MRI or are more readily available for the diagnosis in question, they should not be withheld from a pregnant patient."

Additionally, the risk to the fetus from exposure to ionizing radiation is dependent on the gestational age during exposure (see the Table below from the publication). Exposure to high doses (in excess of 1Gy) that occur during embryogenesis could likely be lethal to the embryo; however, doses this high are not often used for routine diagnostic imaging. The most common adverse events demonstrated after exposure to high doses of radiation are growth restriction, microcephaly and intellectual disability. It is suggested that intellectual disability has been shown at exposures that occur during 8 to 15 weeks' gestation, in the range of 60 to 310 mGy. However, multiple diagnostic x-ray procedures rarely result in ionizing radiation exposure this high. (See the Table below from the publication for fetal radiation doses associated with common radiologic exams.) Fetal anomalies, growth restriction or spontaneous abortion have not been reported in radiation exposure of < 50 mGy, which is a level above the range of exposure for diagnostic procedures. The risk of carcinogenesis after in utero exposure to ionizing radiation is unclear.

For additional information regarding fetal radiation exposure and doses associated with common radiologic exams and teratogenicity refer to Appendix C.

[10] ACOG Committee Opinion. Number 723. October 2017. Guidelines for Diagnostic Imagining During Pregnancy and Lactation. Committee on Obstetric Practice. https://www.acog.org/-/media/project/acog/acogorg/clinical/files/committee-opinion/articles/2017/10/guidelines-for-diagnostic-imaging-during-pregnancy-and-lactation.pdf

Nonclinical Experience[11]
Embryo-fetal development studies in rats and rabbits and the pre/post-natal study in rats exposed to gadopiclenol showed some signs of maternal toxicity in both species at the highest dose but there was no evidence of any teratogenicity in both rats and rabbits.

In a pre/post-natal toxicity study (GDX-33-056), gadopiclenol was administrated intravenously to pregnant/lactating adult female rats (from gestation day (GD) 6 until lactation day (LD) 20) (22 rats/group) at dose levels of 2.5, 5 and 10 mmol/kg/day. Gadopiclenol administration to pregnant/lactating rats was associated with transient clinical observations in all groups receiving gadopiclenol. The effects were considered non-adverse at 2.5 and 5 mmol/kg/day. There was reduced food consumption during the whole gestational period at 5 and 10 mmol/kg/day, and transient reduced body weight gain at 10 mmol/kg/day (with only a transient and minor impact on absolute body weight

Pharmacokinetics studies suggested little placental transfer to pups.

The NOAEL for maternal toxicity was therefore considered to be 5 mmol/kg/d. At this dose level, the NOAEL corresponds to an AUC0-t of 20800 µg.h/mL on GD6 and 11000 µg.h/mL on LD20 (i.e., 37 and 19 times the human dose).

The reader is referred to the full Pharmacology/Toxicology review by Yinka Dina, Ph.D, DARRTS.

Review of Literature
Applicant's Review of Literature
The applicant did not submit a formal review of the literature; however, the applicant submitted a reference to the FDA safety class labeling changes for GBCA's, as well as the recommended class labeling for subsection 8.1.

DPMH's Review of Literature
In November of 2019, DPMH completed a review of multiple gadolinium imaging products with regards to their use during pregnancy. At the time, DPMH provided labeling recommendations for the pregnancy section of GBCA labeling based on a review of literature and professional guidelines. For the purposes of this review, DPMH conducted an updated review of published literature from the 2019 review to present using PubMed and Embase regarding GBCA exposure during pregnancy using the following search terms, "GBCAs and fetal malformations," "GBCAs and spontaneous abortion and miscarriage," "GBCAs and embryo-fetotoxicity." Additional data were not located in published literature.

[11] January 21, 2022, Nonclinical Summary. New Drug Application (NDA) 216986 submission for Gadopiclenol Injection.

According to Micromedex,[12]

> "Gadolinium exposure during early pregnancy was reported in a small number of cases without apparent adverse effects. Late pregnancy exposure was without sequelae in 11 newborns. The American College of Radiology recommended avoidance of intravenous administration of gadolinium-based contrast agents during pregnancy."

Reviewer comment: Refer to the Discussion and Conclusions section below for DPMH recommendations.

LACTATION

Nonclinical Experience[11]

Gadopiclenol, as other GBCAs, is excreted into the breast milk of lactating rats in very small amounts. Milk excretion of gadopiclenol was examined following a single IV administration of (153Gd)-gadopiclenol to lactating female rats at a target dose level of 0.6 mmol/kg. This study did not show an elimination of gadopiclenol in milk. Mean concentrations in all samples were very low, with the highest concentrations at 6 hours post-dose (0.3% of administered dose in pups), with mean concentrations in milk, pups and mammary gland decreasing at 24 hours post-dose (0.2% of the administered dose in pups).

The reader is referred to the full Pharmacology/Toxicology review by Yinka Dina, Ph.D, DARRTS.

Review of Literature

DPMH conducted a review of published literature regarding GBCAs and use during lactation using PubMed, Embase, ReproTox and TERIS, LactMed, and Thomas Hale's book (*Medications and Mothers' Milk*). No new published data were found. See Table 2 below for a summary of guidelines.

In addition, according to previous DPMH reviews for gadolinium imaging products, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in breast milk, and there is limited GBCA gastrointestinal absorption in the breastfed infant.

Table 2. GBCA exposure and breastfeeding guidelines

Organization	Guidelines for breastfeeding
American College of Radiology (ACR) Committee on Drugs and Contrast Media[2]	GBCA's overall have a plasma half-life of approximately 2 hours and are cleared from the body within 24 hours in someone with healthy renal function. In addition, the committee states that available data suggest that it is safe to breastfeed after receiving GBCAs for MRI as a small percentage of gadolinium is excreted into the breast milk and absorbed by the infant stomach.

[12] Gadolinium. Truven Health Analytics LLC. Micromedex.

Micromedex[12]	"Gadopentetate dimeglumine is transferred to human milk in small amounts.[13,14,15] Nineteen lactating women who were given an intravenous dose of gadopentetate dimeglumine showed a mean of 0.009% (range 0.001% - 0.04%) of the maternal dose to be excreted in milk over the following 24 hours.[14] The authors of this study pointed out that this dose is less than 1/100th of the therapeutic dose for neonates, and very little orally administered gadopentetate dimeglumine is believed to be systemically absorbed. For these reasons, they and other commentators have questioned an older recommendation that breastfeeding be delayed for 12 to 24 hours after a maternal exposure to this agent.[13,14,16,17,18,19] The European Society of Uroradiology Contrast Medium Safety Committee recommended in 2013 that lactating women receiving the highest risk gadolinium contrast media should stop breast feeding for 24 hours and discard expressed milk.[20] In 2018, the European Society of Urogenital Radiology guidelines stated breastfeeding may be continued normally after macrocyclic gadolinium-based contrast agents.[21] Macrocyclic agents tend to be more stable than linear forms.[21,22] The linear agents are Gadodiamide, Gadopentetate dimeglumine, and Gadoversetamide. No comment on the use of the linear agents was included in the guidelines."
ESUR Guidelines on Contrast Agents (European Society of Urogenital Radiology)[3]	Lactating patients may wish to discard the breastmilk 24 hours after GBCA contrast exposure however this is not necessary and they should discuss the best option with their physician.

[13] Rofsky NM, Weinreb JC, Litt AW: Quantitative analysis of gadopentetate dimeglumine excreted in breast milk. J Magn Reson Imaging 1993;3:131-2.
[14] Schmiedl U, Maravilla KR, Gerlach R, Dowling CA: Excretion of gadopentetate dimeglumine in human breast milk. AJR Am J Roentgenol 154:1305-6, 1990.
[15] Kubik-Huch RA, Gottstein-Aalame NM, Frenzel T, Seifert B, Puchert E, Wittek S, Debatin JF: Gadopentetate dimeglumine excretion into human breast milk during lactation. Radiology 2000;216:555-8.
[16] Hylton NM: Suspension of breast-feeding following gadopentetate dimeglumine administration. Radiology 2000;216:325-6.
[17] Webb JA, Thomsen HS, Morcos SK; Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol 2005;15:1234-1240.
[18] American College of Radiology Committee on Drugs and Contrast Media. Administration of contrast media to women who are breast-feeding. In ACR manual on contrast media. 2020, pg. 101. http://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf
[19] American College of Obstetricians and Gynecologists` Committee on Obstetric Practice. Committee Opinion No. 656: Guidelines for Diagnostic Imaging During Pregnancy and Lactation. Obstet Gynecol. 2016 Feb;127(2):e75-80. doi:10.1097/AOG.0000000000001316. PubMed PMID: 26942391.
[20] Webb JAW, Thomsen HS. 2013. Gadolinium contrast media during pregnancy and lactation. Acta Radiol 54: 599-600.
[21] European Society of Urogenital Radiology. ESUR guidelines on contrast media. 2019;Version 10.0. http://www.esur.org/fileadmin/content/2019/ESUR_Guidelines_10.0_Final_Version.pdf
[22] Ranga A, Agarwal Y, Garg KJ. Gadolinium based contrast agents in current practice: Risks of accumulation and toxicity in patients with normal renal function. Indian J Radiol Imaging. 2017 Apr-Jun;27(2):141-147. doi:10.4103/0971-3026.209212. PubMed PMID: 28744073; PubMed Central PMCID:PMC5510310.

American College of Obstetricians and Gynecologists[10]	No interruption in breastfeeding needed after exposure to gadolinium agents.

Reviewer comment: Refer to the Discussion and Conclusions section below for DPMH recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience[11]

No effect was seen on reproductive performance and fertility in male and female rats exposed to gadopiclenol in doses 62 times the human equivalent.

The reader is referred to the full Pharmacology/Toxicology review by Yinka Dina, Ph.D, DARRTS.

Review of Literature

DPMH conducted a review of published literature with regards to GBCAs and fertility, and no data were found. The sponsor has recommended omitting subsection 8.3 Female and Males of Reproductive Potential as there are no available human data and reproductive studies in rats showed no effect on fertility.

Reviewer comment: Refer to the Discussion and Conclusions section below for DPMH recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Embryo-fetal development studies in rats and rabbits and the pre/post-natal study in rats with gadopiclenol showed some signs of maternal toxicity in both species at the highest dose, but there was no evidence of any teratogenicity in both rats and rabbits. In November of 2019, DPMH completed a review of multiple gadolinium imaging products with regards to their use during pregnancy. At the time, DPMH provided labeling recommendations for pregnancy sections of all GBCA labeling based on a review of literature and professional guidelines. The Agency approved updated language for all marketed GBCAs, which included the recommended safety labeling changes related to pregnancy. No new information was identified in this review.

Since there are no new safety concerns with gadopiclenol or other approved GBCAs , DPMH does not recommend any postmarking pregnancy safety studies at this time.

Lactation

Gadopiclenol is present in the milk of lactating rats. According to published lactation data on other GBCAs, 0.01 to 0.04% of the maternal gadolinium dose is excreted in breast milk, and there is limited GBCA gastrointestinal absorption in the breastfed infant. No safety concerns related to exposure to gadopiclenol and use during lactation have been identified, and guidelines state that there is no reason to interrupt breastfeeding. No new safety information was identified in this review. Since there are no new safety concerns regarding the use of gadopiclenol or other approved GBCAs during lactation, DPMH does not recommend any postmarketing clinical lactation study at this time.

Females and Males of Reproductive Potential

Reproductive studies showed no effect on fertility in male and female rats exposed to gadopiclenol in doses 62 times the human equivalent. In addition, there are no human data on the effects of gadopiclenol on fertility. DPMH does not recommend pregnancy testing or contraception requirements for gadopiclenol. Subsection 8.3 Females and Males of Reproductive Potential will be omitted from labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

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APPENDICES

APPENDIX A - Applicant's proposed labeling language
APPENDIX B - Former of previous DPMH review of gadolinium products and pregnancy exposure
APPEDNIX C – Common Fetal Radiation Doses and Teratogenicity

APPENDIX A – Applicant's Proposed Labeling

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APPENDIX B – Summary of DPMH's prior review of literature of gadolinium products and pregnancy[23]

- A prospective cohort study of 26 women who were exposed to gadopentetate dimeglumine [a gadolinium derivative approved for use as a contrast agent with MRI to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues] in the first trimester reported 23 full term births without any malformations, two miscarriages, and one elective termination.[24]

- One case report described a successful pregnancy in a patient with multiple sclerosis who was inadvertently injected intravenously with gadopentetate dimeglumine during very early pregnancy.[25]

- No adverse effects were detected at birth in eleven newborns exposed to gadopentetate dimeglumine prenatally during the second and third trimesters as part of a placental imaging study.[26]

- A case series reported normal pregnancy outcomes for a woman who was three months pregnant and a woman who was five months pregnant who received gadopentetate dimeglumine to establish a diagnosis of Crohn's disease.[27]

- There were no adverse outcomes in the newborns of 15 pregnant women who were exposed to gadolinium-enhanced MRI to diagnose placenta accrete and placenta percreta.[28]

- 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.[29]

- 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.[30]

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[23] Adapted from Appendix 1 of November 7, 2019, DPMH literature and labeling review for multiple gadolinium imaging products, Omniscan (NDAs 20123, 22066), Magnevist (NDA 19596), Gadavist (NDA 201277), Eovist (22090), ProHance (NDAs 20131, 21489), MultiHance (NDAs 21357, 21358), Ablavar (NDA 21711), Optimark (NDAs 20937, 20975, 20976), Dotarem (204781); Erica Radden, MD, Medical Officer, DARRTS Reference ID 4514372.

[24] De Santis M, Straface G, Cavaliere AF, Carducci B, Caruso A: Gadolinium periconceptional exposure: pregnancy and neonatal outcome. Acta Obstet Gynecol Scand 2007;86:99- 101.

[25] Barkhof F, Heijboer RJ, Algra PR: Inadvertent i.v. administration of gadopentetate dimeglumine during early pregnancy [letter]. Am J Roentgenol 158: 1171, 1992.

[26] Marcos HB, Semelka RC, Worawattanakul S: Normal placenta: gadolinium-enhanced dynamic MR imaging. Radiology 1997; 205:493-6.

[27] Shoenut JP, et al. MRI in the diagnosis of Crohn's Disease in two pregnant women. J Clin Gastroenterology 1993; 17(3):244-7.

[28] Jaraquemada JM, Bruno C: Gadolinium-enhanced MR imaging in the differential diagnosis of placenta accreta and placenta percreta. Radiology 2000; 216:610-611.

[29] 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.

[30] 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.

- 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.[31]

- A retrospective cohort sutdy evaluated over 1.4 million Ontario pregannies that resulted in live birth or stillbirth (after 20 weeks of gestation) between April 27, 2003, and March 4, 2015. The study used administrative healthcare data from Ontario, Canada and propensity score-weighted analysis to examine outcomes after MRI or GBCA exposure in pregnancy. The author found no increased risk for congenital anomalies, neoplasm, or vision or hearing loss. Furthermore, the hazard ratio for Nephrogenic Systemic Fibrosis (NSF)-like outcomes (1.00, 95% CI, 0.33 to 3.02) was not statistically significant. Also, exposure to MRI during the first trimester of pregnancy compared with non-exposure was not associated with increased risk of harm to the fetus or in early childhood.[32]

    - The study identified 397 pregnancies with GBCA exposure, and out of these pregnancies, found four stillbirths (after 20-week gestation) and three neonatal deaths (within 28 days of birth). Ray, et al. estimated incidence at 17.6 stillbirths or neonatal deaths per 1000 pregnancies. Furthermore, when compared to more than 1.4 million stillborn or live born infants without prenatal MRI, Ray, et al. estimated the covariate-adjusted risk difference at 47.5 per 1000 (95% CI 9.7 to 138.2 per 1000). The authors also concluded an increased risk for a broad set of rheumatological, inflammatory, or infiltrative skin conditions with gadolinium MRI at any time during pregnancy [occurred in 123 vs 384,180 births (adjusted HR, 1.36; 95% CI, 1.09 to 1.69) for an adjusted risk difference of 45.3 per 1000 person-years (95% CI, 11.3 to 86.8)].
    - The Office of Surveillance and Epidemiology (OSE) evaluated this study in November 2016, and noted that the author reports the following limitations with the study: (1) limited power, (2) type I error rate not adjusted for multiple comparisons, (3) residual confounding unaddressed by propensity score weighting, (4) missing information about the medical indication for prenatal MRI, and (5) live-born infants frequently not followed for four complete years after birth. Additionally, the study does not delineate use of pecific GBCAs. Regarding the evaluation of the broad set of rheumatological, inflammatory, or infiltrative skin conditions, OSE commented that the extreme heterogeneity of the collection of diagnostic codes severely limited the meaningfulness and interpretability of results because the underlying disease may confound the findings that were attributed to GBCA use reported by Ray for this broad outcome category. OSE also noted that despite its large size, Ray, et al. did not equivocally establish the safety or the risks of GBCAs in pregnancy and found moderate risk of bias for the outcome of stillbirth or neonatal death. Nevertheless, given the limited data previously available from small cohort studies and case reports, they advised that inclusion of the quantitative results in Ray's report about stillbirth or neonatal death in the pregnancy section of labeling for GBCA products should be considered.

[31] 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.
[32] Ray, JG, MJ Vermeulen, A Bharatha, WJ Montanera, and AL Park, 2016, Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes, JAMA, 316(9):952-961, doi:10.1001/jama.2016.12126.

APPENDIX C – Common Fetal Radiation Doses and Teratogenicity

Table C-1. ACOG – Fetal Radiation Doses Associated with Common Radiologic Exams (Table 3 page 5 of ACOG 2017 Guidelines for Diagnostic Imaging During Pregnancy)

Type of Examination	Fetal Dose* (mGy)
Very low-dose examinations (<0.1 mGy)	
Cervical spine radiography (anteroposterior and lateral views)	<0.001
Head or neck CT	0.001–0.01
Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
Low- to moderate-dose examinations (0.1–10 mGy)	
Radiography	
Abdominal radiography	0.1–3.0
Lumbar spine radiography	1.0–10
Intravenous pyelography	5–10
Double-contrast barium enema	1.0–20
CT	
Chest CT or CT pulmonary angiography	0.01–0.66
Limited CT pelvimetry (single axial section through the femoral heads)	<1
Nuclear medicine	
Low-dose perfusion scintigraphy	0.1–0.5
Technetium-99m bone scintigraphy	4–5
Pulmonary digital subtraction angiography	0.5
Higher-dose examinations (10–50 mGy)	
Abdominal CT	1.3–35
Pelvic CT	10–50
^{18}F PET/CT whole-body scintigraphy	10–50

Abbreviations: CT, computed tomography; PET, positron emission tomography.

*Fetal exposure varies with gestational age, maternal body habitus, and exact acquisition parameters.

Note: Annual average background radiation = 1.1–2.5 mGy, ^{18}F = 2-[fluorine-18]fluoro-2-deoxy-D-glucose.

Modified from Tremblay E, Therasse E, Thomassin-Naggara I, Trop I. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. Radiographics 2012;32:897–911.

Table C-2. ACOG – Effects of Gestational Age and Radiation Dose on Radiation-Induced Teratogenesis (corresponds to Table 2 page 4 of ACOG 2017 Guidelines for Diagnostic Imaging During Pregnancy)

Gestational Period	Effects	Estimated Threshold Dose*
Before implantation (0–2 weeks after fertilization)	Death of embryo or no consequence (all or none)	50–100 mGy
Organogenesis (2–8 weeks after fertilization)	Congenital anomalies (skeleton, eyes, genitals)	200 mGy
	Growth restriction	200–250 mGy
Fetal period	**Effects**	**Estimated Threshold Dose***
8–15 weeks	Severe intellectual disability (high risk)†	60–310 mGy
	Intellectual deficit	25 IQ-point loss per 1,000 mGy
	Microcephaly	200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy*

*Data based on results of animal studies, epidemiologic studies of survivors of the atomic bombings in Japan, and studies of groups exposed to radiation for medical reasons (eg, radiation therapy for carcinoma of the uterus).

†Because this is a period of rapid neuronal development and migration.

Modified from Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 2007;27:1705–22.

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/s/

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MIRIAM C DINATALE
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LYNNE P YAO
05/31/2022 08:39:12 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 26, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216986
Product Name, Dosage Form, and Strength:	Gadopiclenol[a] Injection, 1.5 mmol/3 mL (0.5 mmol/mL), (b) (4) mmol/7.5 mL (0.5 mmol/mL), 5 mmol/10 mL (0.5 mmol/mL), 7.5 mmol/15 mL (0.5 mmol/mL), 15 mmol/30 mL (0.5 mmol/mL), 25 mmol/50 mL (0.5 mmol/mL), and 50 mmol/100 mL (0.5 mmol/mL)
Product Type:	Single Ingredient Product and Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Guerbet LLC (Guerbet)
FDA Received Date:	January 21, 2022, March 1, 2022, and April 7, 2022
OSE RCM #:	2022-152
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

[a] A proprietary name for this application has not been determined yet. As such, the product will be referred to as Gadopiclenol Injection throughout this document.

1 REASON FOR REVIEW

Guerbet LLC (Guerbet) submitted a 505(b)(1) application under NDA 216986 for Gadopiclenol Injection on January 21, 2022. Gadopiclenol Injection is a gadolinium-based contrast agent proposed in adults and children aged 2 years and older for contrast enhanced magnetic resonance imaging (MRI) to (b) (4) lesions in the Central Nervous System (brain, spine and (b) (4) tissues), and the Body (head and neck, thorax (b) (4), abdomen (b) (4), pelvis (b) (4), and musculo-skeletal system). We evaluated the proposed Gadopiclenol Injection prescribing information, medication guide, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), medication guide, container labels, and carton labeling to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. We note the proposed product will be available in a pharmacy bulk package, single-dose vials, and pre-filled syringes. Separate PIs were submitted for the vials/pre-filled syringe and the pharmacy bulk package. We note the Division made the determination to include all the presentations in the same PI. We find this proposal acceptable as long as the preparation section of the PI clearly states how each presentation needs to be used. The pharmacy bulk package product is not used for direct administration but is used to withdraw individual doses as needed during a 24-hour period after initial puncture of the package with a suitable transfer device.

(b) (4)

After discussion with the Division, we determined the strength should only be presented in mmol/mL which is consistent with the carton and container labels.

We identified areas in the proposed prescribing information, medication guides as well as the single-dose vial container label, single-dose syringe container label, pharmacy bulk package container label, single-dose vial carton labeling, single-dose syringe carton labeling, pharmacy bulk package carton labeling, single-dose vial case labeling, single-dose syringe case labeling, and pharmacy bulk package case labeling that could be revised to improve clarity and readability of important information. We provide our recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant.

4 CONCLUSION & RECOMMENDATIONS

Our review concludes the proposed Gadopiclenol Injection prescribing information, medication guide, single-dose vial container label, single-dose syringe container label, pharmacy bulk package container label, single-dose vial carton labeling, single-dose syringe carton labeling, pharmacy bulk package carton labeling, single-dose vial case labeling, single-dose syringe case labeling, and pharmacy bulk package case labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Guerbet LLC so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. As currently presented, the highlights of dosage and administration section is presented as a paragraph. We recommend breaking up the information into bullet points in order to increase readability. The first bullet should read “Recommended dose for adults and pediatric patients is 0.1 mL/kg body weight (equivalent to 0.05 mmol/kg).”. The second bullet should read “Administer as an intravenous bolus injection.”.

2. Dosage Forms and Strengths

a. We note the dosage form is not presented, the strength should be revised, and the package type terms are not included. We recommend revising to read “Injection: 0.5 mmol/mL of gadopiclenol in single-dose vials, single-dose prefilled syringes, and pharmacy bulk packages. (3)”.

B. Prescribing Information

1. Section 2: Dosage and Administration

a. As currently presented, [redacted] in order to avoid confusion.

b. We note in the sixth bullet under Section 2.2 Administration Instructions that the end user is instructed to follow the injection with a flush of [redacted] We recommend removing the use of [redacted] and replacing it with "0.9% Sodium Chloride Injection, USP".

c. We note [redacted] this information is not needed here.

d. As currently presented, there is not a bullet point under "Vial" and "Pre-filled syringe" regarding discarding any unused portion. We recommend including a bullet under both sections that states "Discard any unused portion".

e. We note the last bullet under "Pre-filled syringe" states "Prime intravenous line before use". We recommend moving this bullet to the top portion of Section 2.2 Administration Instructions as the fifth bullet.

2. Section 3: Dosage Forms and Strengths

a. As currently presented, we note the dosage form is not and this section lacks a physical description. We recommend revising this section to read "Injection: [redacted], clear, colorless to yellow aqueous solution [redacted]...".

b. As currently presented, the package type terms are not included. We recommend revising "vials" to read "single-dose vials" and revising "prefilled syringes" to read "single-dose prefilled syringes".

3. Section 16: How Supplied/Storage and Handling

a. We note Section 16 How Supplied/Storage and Handling contains a subheading for storage, but it lacks a subheading for how supplied. We recommend including a subheading for the How Supplied information.

b. As currently presented, Section 16 How Supplied/Storage and Handling lacks a physical description of the proposed product. We recommend including a statement at the beginning of the how supplied information that reads "Gadopiclenol Injection is a [redacted] clear, colorless to yellow aqueous solution [redacted]".

C. Medication Guide

1. We note the second bullet under 'What is the most important information…" states [redacted] We recommend removing this bullet from the Medication Guide as this information is not needed.

4.2 RECOMMENDATIONS FOR GUERBET LLC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Labels and Carton Labeling)

1. We note the proprietary name for this product has not been determined yet. As such, we recommend replacing the proprietary name with "Tradename" as a placeholder until a proprietary name has been conditionally approved.
2. As currently presented, the proposed container labels, carton labeling and case labeling prominently display the net quantity volume [redacted]. We recommend decreasing the prominence of the volume on each of the labels and labeling by [redacted] presenting the volume in the black font used elsewhere on the labels to prevent confusion.
3. We note the total strength is presented [redacted], and the strength per mL is presented in black font. The strength should be expressed as the total quantity per total volume followed by the concentration per mL in accordance with USP General Chapter <7>. For example, present the strength as "50 mmol/100 mL (0.5 mmol/mL)". We recommend presenting the strength so that the total quantity per total volume is larger than concentration per mL to prevent healthcare practitioner confusion when determining the quantity of drug in the container. Additionally, we recommend increasing the prominence of the total strength by utilizing a colored box around the total strength and the strength per mL.

B. Carton Labeling and Container Labels - Vials

1. As currently presented, the proposed vial container labels contain the package type term "Single Use Vial. Discard Unused Portion.". We recommend revising the package type term on the vial container labels to read "Single Dose Vial. Discard Unused Portion.".

C. Carton Labeling (Single-Dose Vials, Single-Dose Prefilled Syringe, and Pharmacy Bulk Package)

1. We note there is a medication guide proposed for this product and currently the carton labeling does not include a statement regarding dispensing the Medication Guide to each patient. We recommend including the statement "Dispense the enclosed Medication Guide to each patient" on the principal display panel per 21 CFR 208.24(d).

D. Case Labeling (Single-Dose Vials and Pharmacy Bulk Package)

1. As currently presented, the single-dose vial case labeling and Pharmacy Bulk Package case labeling contain the statement "XX vials of XX mL". We recommend revising this statement to read "XX x XX mL vials". For Example, we recommend revising "10 vials of 10 mL" to read "10 x 10 mL vials".

E. Pharmacy Bulk Package Container Label

1. We note the package type term [redacted] (b) (4) is presented on the the proposed 30 mL and 50 mL pharmacy bulk package container label. We recommend revising the package type term to read "multiple dose vial" to align with the information presented in the PI and placing the package type on the principal display panel.

2. As currently presented, the proposed Pharmacy Bulk Package Container Label lacks space to include when to discard the bottle after opening. We note the contents of the Pharmacy Bulk Package container must be used within 24 hours after the initial puncture. We recommend including a box on the proposed Pharmacy Bulk Package Container Label to include spaces for "Discard After __/__/__" and "at __:__".

F. Pharmacy Bulk Package Carton Labeling

1. We note the statements [redacted] (b) (4) and [redacted] (b) (4) are presented on different panels of the proposed pharmacy bulk package carton labeling. We recommend presenting both of these statements on the same panel of the proposed pharmacy bulk package carton labeling.

2. As currently presented, the proposed pharmacy bulk package carton labeling contains the package type term [redacted] (b) (4). We recommend revising the package type term to read [redacted] (b) (4) to align with the pharmacy bulk package PI.

G. Pharmacy Bulk Package Case Labeling

1. We note the proposed pharmacy bulk package case labeling contains the statements "[redacted] (b) (4)". We also note the proposed 30 mL, 50 mL, and 100 mL pharmacy bulk package are multiple dose vials. We recommend removing the statements "[redacted] (b) (4)" and revising "[redacted] (b) (4)" to read [redacted] (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gadopiclenol Injection received on January 21, 2022 from Guerbet LLC.

Table 2. Relevant Product Information for Gadopiclenol Injection	
Initial Approval Date	N/A
Active Ingredient	Gadopiclenol
Indication	Gadolinium-based contrast agent indicated in adults and children age 2 years and older for contrast enhanced magnetic resonance imaging (MRI) to (b) (4) lesions in: • the Central Nervous System (brain, spine and (b) (4) tissues) • the Body (head and neck, thorax (b) (4), abdomen (b) (4), pelvis (b) (4), and musculo-skeletal system)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	1.5 mmol/3 mL (0.5 mmol/mL), (b) (4) mmol/7.5 mL (0.5 mmol/mL), 5 mmol/10 mL (0.5 mmol/mL), 7.5 mmol/15 mL (0.5 mmol/mL), 15 mmol/30 mL (0.5 mmol/mL), 25 mmol/50 mL (0.5 mmol/mL), and 50 mmol/100 mL (0.5 mmol/mL)
Dose and Frequency	The recommended dose of Gadopiclenol Injectionis 0.1 mL/kg body weight (equivalent to 0.05 mmol/kg) for adult and pediatric patients (2 years of age and older) administered as an intravenous bolus injection.
How Supplied	Gadopiclenol Injection is supplied in the following presentations: • Vial (glass) o 3 mL vial (filled in 10 mL-vial) packed in a carton box of 1 and 10 o 7.5 mL vial (filled in 10 mL-vial) packed in a carton box of 1 and 10 o 10 mL vial (filled in 10 mL-vial) packed in a carton box of 1 and 10 o 15 mL vial (filled in 20 mL-vial) packed in a carton box of 1 and 10 • Prefilled syringe (plastic) o 7.5 mL prefilled syringe (filled in 15 mL-syringe) packed in a carton box of 1 and 10

	○ 10 mL prefilled syringe (filled in 15 mL-syringe) packed in a carton box of 1 and 10 ○ 15 mL prefilled syringe (filled in 15 mL-syringe) packed in a carton box of 1 and 10 • Pharmacy Bulk Package Vial ○ 30 mL vial (filled in 50 mL-vial) packed in a carton box of 1 and 25 ○ 50 mL vial (filled in 50 mL-vial) packed in a carton box of 1 and 25 ○ 100 mL vial (filled in 100 mL-vial) packed in a carton box of 1, 6 and 12
Storage	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP, Controlled Room Temperature (CRT)]. Pre-filled syringes must not be frozen. (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 18, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, gadopiclenol injection. Our search identified 1 previous review[b], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Kane, D. Comparative Analyses and Use-Related Risk Analysis Review for Gadopiclenol (IND 123673). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 MAR 10. RCM No.: 2021-2338.

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Gadopiclenol Injection labels and labeling submitted by Guerbet LLC.

- Vial Container Labels received on March 1, 2022
- Prefilled Syringe Container Label received on March 1, 2022
- Pharmacy Bulk Package Vial Container Label received on March 1, 2022
- Vial Carton Labeling received on March 1, 2022
- Prefilled Syringe Carton Labeling received on March 1, 2022
- Pharmacy Bulk Package Carton Labeling received on March 1, 2022
- Vial Case Labeling received on March 1, 2022
- Prefilled Syringe Case Labeling received on March 1, 2022
- Pharmacy Bulk Package Case Labeling received on March 1, 2022
- Prescribing Information and Medication Guide (Image not shown) received on January 22, 2022, available from \\CDSESUB1\evsprod\nda216986\0001\m1\us\114-labeling\114a-draft-label\(b) (4)-clean-draft-uspi-15dec2021.docx
- Pharmacy Bulk Package Prescribing Information and Medication Guide (Image not shown) received January 22, 2022, available from \\CDSESUB1\evsprod\nda216986\0001\m1\us\114-labeling\114a-draft-label\(b) (4) clean-draft-uspi-pbp-15dec2021.docx

G.2Label and Labeling Images

- Vial Container Labels

(b) (4)

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

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Memorandum

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

Date: May 16, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, Pharm.D.
Clinical Analyst, DCN

To: Sharon Thomas, RPM
DIRM

Subject: IRT Consult to IND-216986 (SDN001)

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

This memo responds to your consult to us dated 3/4/2022 regarding the sponsor's proposed label. We reviewed the following materials:

- Previous IRT review for IND-123673 dated 05/28/2019 in DARRTS (link);
- Previous IRT review for IND-123673 dated 12/06/2017 in DARRTS (link); and
- Sponsor's proposed product label (SN0001; link).

1 IRT Responses

The sponsor characterized the risk of QT prolongation of gadopiclenol in a thorough QT study (Study # GDX-44-006). The IRT previously reviewed sponsor's thorough QT study report (Dt: 05/28/2019) and concluded that no significant QTc prolongation effect of gadopiclenol was detected (Section 3).

IRT's Response:

No QT labeling language was proposed by the sponsor in the label submitted to SDN001 (link). Our proposed text is highlighted below (*addition*, *deletion*). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology

At a dose 6 times the maximum approved recommended dose, <TRADENAME> does not prolong the QT interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

2 Internal Comments to the Division

- *None.*

3 Background

Guerbet LLC. is developing a new contrast agent, gadopiclenol, for magnetic resonance imaging (MRI). Gadopiclenol ((b) (4), P03277; MW: 970.11 g/mol) is a non-ionic macrocyclic, paramagnetic, third generation gadolinium (Gd) complex developed for intravenous administration. Refer to previous IRT review for IND-123673 dated 12/06/2017 and 05/28/2019 in DARRTS.

The product is formulated as a sterile, aqueous, injectable solution (Vial or PFS) containing 485.1 mg/mL gadopiclenol (equivalent to 0.5 mmol/mL; 78.6 mg/mL of gadolinium). The proposed maximum recommended dose includes a single intravenous bolus (2 mL/s) injection at 0.1 mL/kg body weight (equivalent to 0.05 mmol/kg; 2 years of age and older). The peak gadopiclenol concentrations of 525 µg/mL (C10: 363 µg/mL, half-life: 1.5 to 1.9 h) were observed following single intravenous dose of 0.05 mmol/kg body weight. The sponsor states that the pharmacokinetic profile of gadopiclenol was similar between adult and pediatric patients with slightly lower exposures (C10: ~303 µg/mL for 2 to 6 years; POP-PK predicted) of gadopiclenol were observed with age and proposed no dose adjustment pediatric population (Study # GDX-44-007).

Sponsor claims that gadopiclenol is not significantly metabolized (including CYP450 enzymes) and highlights that it has a low drug interaction potential as a victim drug. Renal impairment study indicated increased exposures of gadopiclenol with decreasing renal function (AUC: 54% in mild, 148% moderate, and 769% in severe) as urinary excretion is the major route of elimination. The peak gadopiclenol concentrations of 1251 µg/mL (half-life: 11 h) were observed following single intravenous dose of 0.1 mmol/kg body weight in subjects with severe renal impairment (Study # GDX-44-005). The sponsor proposed no dose adjustment in subjects with renal impairment.

Previously, the IRT reviewed the sponsor's thorough QT study protocol. Refer to previous IRT review for IND-123673 dated 12/06/2017 in DARRTS. Subsequently, the sponsor conducted a single center, randomized, cross-over, double-blind, placebo-controlled, positive-controlled (open-label), thorough QT study in healthy subjects (Study # GDX- 44-006). The study utilized cross-over (4 period × 4 sequence) design with four treatment arms 1) therapeutic dose (single dose, 0.1 mmol/kg; IV bolus 2 mL/s), 2) supra-therapeutic dose (single dose, 0.3 mmol/kg; IV bolus 2 mL/s), 3) placebo (single dose, NaCl 0.9%; IV bolus 2 mL/s), and 4) moxifloxacin (single dose, 400 mg film-coated tablets) and four sequences (n=48; 12/sequence;) according to a Williams design. Refer to previous IRT review for IND-123673 dated 05/28/2019 in DARRTS (*previous review*; link).

No significant QTc prolongation effect of gadopiclenol (P03277; 0.1 mmol/kg IV and 0.3 mmol/kg; intravenous administration) was detected in the TQT study. The highest dose evaluated

(single dose, 0.3 mmol/kg administered intravenously as 2 mL/s) covers the clinically relevant worst-case exposure scenario (renal impairment; Section 3.1 of previous review). The data were analyzed using central tendency analysis as the primary analysis, which did not suggest that gadopiclenol is associated with significant QTc prolonging effect (see Table 1 for overall results). The sponsor's exposure-response analysis indicated a concentration dependent increase in ΔQTcF with a slight positive slope of 0.0011 msec/µg/mL. The model predicted ΔΔQTcF (upper confidence interval) values of 2.23 (3.26) msec at the mean peak concentrations for the highest dose studied (0.3 mmol/kg of gadopiclenol: geomean Cmax ~2491 µg/mL) following a single IV administration. The findings of this analysis were further supported by the available nonclinical data (Section 3.1 of previous review), and categorical analysis (Section 4.4 of previous review).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	**Treatment**	**Time** (h)	**ΔΔQTcF** (msec)	**90% CI** (msec)
QTc	0.1 mmol/kg IV	3.00	2.1	(0.2, 4.0)
QTc	0.3 mmol/kg IV	0.08	5.1	(3.2, 7.0)

For further details on the FDA analysis, please see Section 4.3 of previous review.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov.

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