CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216986Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216986
PDUFA Goal Date	Sept 21, 2022
OSE RCM #	2022-153
Reviewer Name(s)	Somya Dunn, MD
Team Leader	Carolyn Tieu, Pharm.D., MPH
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	Sept 20, 2022
Established Name	Gadopiclenol
Trade Name	Elucirem
Name of Applicant	Guerbet Group, France
Therapeutic Class	Gadolinium-based contrast agent
Dosing Regimen	0.05 mmol/kg body weight (equivalent to 0.1 mL/kg body weight) administered intravenously at approximately 2 mL/sec

Table of Contents

EXECUTIVE SUMMARY 3

1 Introduction 3

2 Background 3

2.1 Product Information 3

2.2 Regulatory History 4

3 Therapeutic Context and Treatment Options 4

3.1 Description of the Medical Condition 4

3.2 Description of Current Treatment Options 5

4 Benefit Assessment 6

5 Risk Assessment & Safe-Use Conditions 8

5.1 Death and Serious Adverse Events 8

5.2 Adverse Events of Special Interest 8

6 Expected Post Market Use 9

7 Proposed Risk Management Activities 9

8 Discussion of Need for a REMS 9

9 Conclusion & Recommendations 9

10 References 10

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Elucirem (gadopiclenol) is necessary to ensure the benefits outweigh its risks. Guerbet Group (the Applicant) submitted a New Drug Application (NDA) 216986 for Elucirem with the proposed indication for adult and pediatric patients aged two years and older for use with magnetic resonance imaging (MRI) to detect and visualize lesions with abnormal vascularity in:

- the central nervous system (brain, spine, and associated tissues),
- the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system).

The risks associated with Elucirem include nephrogenic systemic fibrosis, hypersensitivity reactions, gadolinium retention, acute kidney injury, extravasation and injection site reactions, and interference with visualization of lesions visible with non-contrast MRI. The Applicant did not propose a REMS to address these risks.

DRM has determined that a REMS is not necessary to ensure the benefits of Elucirem. The risks are known class wide risks and there were no unexpected adverse events identified in the clinical program. Similar to other drugs in the same class, the risk of nephrogenic systemic fibrosis will be described in a Boxed Warning and the remaining risks will be described in the Warning and Precaution and Medication Guide sections of Elucirem Prescribing Information (PI) label.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for Elucirem (gadopiclenol) New Drug Application (NDA) 216986 to ensure the benefits outweigh the risks. The Applicant submitted NDA 216986 for Elucirem with a proposed indication for adult and pediatric patients aged two years and older for use with magnetic resonance imaging (MRI) to detect and visualize lesions with abnormal vascularity in:

- the central nervous system (brain, spine, and associated tissues),
- the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system).

This application is under review in the Division of Imaging and Radiation Medicine. The Applicant did not submit a REMS with this application.

2 Background

2.1 PRODUCT INFORMATION

Most approved Gadolinium-based Contrast Agent (GBCAs) are intravenously administered polar molecules that distribute via the circulatory system into the extracellular fluid and have poor ability to cross an intact blood-brain barrier. As a result, the contrast accumulates at higher concentration in areas where there is increased blood flow and accumulation of extracellular fluid which occurs in many inflammatory and neoplastic pathologic processes. GBCAs are used in contrast-enhanced MRI to aid in a variety of diagnostic purposes including tumor detection, brain injury, stroke, aneurysms, spinal cord disorders and musculoskeletal injuries.[1] Administration of GBCA enables lesions to be better characterized by the patterns of signal enhancement produced by the contrast agent.

Elucirem is new macrocylic pyclen-based contrast agent GBCA.[a] The paramagnetic metal gadolinium (Gd3+) is the element responsible for the enhancement effect of GBCA. The recommended dose of Elucirem for adult and pediatric patients aged two years and older is 0.05 mmol/kg actual body weight (BW) (equivalent to 0.1 mL/kg BW) administered intravenously at approximately 2 mL/sec.[b] It would be administered in radiology suites and departments in both outpatient and inpatient healthcare facilities. Elucirem is not marketed in any other countries.

GBCAs have a Boxed Warning for nephrogenic systemic fibrosis (NSF) and are known to increase the risk for NSF among patients with impaired elimination of GBCAs.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 216986 relevant to this review:

1/21/22:	NDA 216986 received and a priority review was granted based on unmet medical need as there are currently no U.S. approved and marketed MRI contrast agents indicated for musculoskeletal lesion visualization
3/22/22:	NDA was filed
5/10/22:	Midcycle Communication was sent to the Applicant and the Agency communicated that although the review was still ongoing, no REMS was determined to be required at that time.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

MRI is an imaging modality that measures hydrogen activity in a magnetic field after exposure to radiofrequency energy. MRI is used very widely for anatomic imaging and can noninvasively display high-resolution images with high quality tissue contrast. It is one of the primary imaging technologies for detecting pathology in soft tissues, such as meniscal, ligament and tendon tears, and in occult bone injuries.[2] In the brain, MRI can differentiate between white and grey matter enabling diagnosis of life-threatening conditions such as aneurysms and tumors.[c] Also in contrast to computerized tomography (CT) imaging, MRI does not use radiation caused by x-rays and as a result is preferred when frequent imaging is needed to follow a disease process, especially in the brain.[3] Millions of MRI scans are performed in the United States every year and GBCAs are often used to alter the contrast of the image and improve diagnostic ability.[4] [d]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

At this time there are six FDA approved GBCAs in the US, as shown in Table 1. All of the approved GBCAs are labelled for visualization of central nervous system (CNS) lesions with the exception of gadoxetate disodium. All of these GBCAs have a Box Warning for NSF. In addition, their PI include warnings for the other class wide safety concerns of hypersensitivity reactions, gadolinium retention, acute kidney injury, extravasation and injection site reactions, and interference with visualization of lesions visible with non-contrast MRI.

Table 1. FDA approved MRI contrast agents

Established Name	Proprietary Name	Structural Features	Indications
gadobenate dimeglumine	MultiHance	Linear, ionic	For 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 For MRA to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease
gadobutrol	Gadavist	Macrocyclic, nonionic	To detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system in adult and pediatric patients, including term neonates To assess the presence and extent of malignant breast disease in adult patients To evaluate known or suspected supra-aortic or renal artery disease in adult and pediatric patients, including term neonates To assess myocardial perfusion (stress, rest) and late gadolinium enhancement in adult patients with known or suspected coronary artery disease
gadodiamide	Omniscan	Linear, nonionic	To visualize lesions with abnormal vascularity in the brain, spine, and associated tissues To facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space
gadoterate meglumine	Dotarem	Macrocyclic, ionic	For intravenous use with 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
gadoteridol	ProHance	Macrocyclic, nonionic	To visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues in adults and pediatric patients over 2 years of age To visualize lesions in the head and neck in adults
gadoxetate disodium	Eovist	Linear, ionic	For use in MRI of the liver to detect and characterize lesions in patients with known or suspected focal liver disease

Source: FDA Unireview for Elucirem, Table XX. Review in progress. Accessed Sept 13 2022.
Abbreviations: CNS = central nervous system, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging

4 Benefit Assessment

The effectiveness of Elucirem for lesion visualization was evaluated in two prospective, double-blind, randomized, crossover clinical studies. Study 1 (NCT03996447) was conducted in adults with known or highly suspected CNS lesions with focal areas of disruption of the blood-brain barrier. Study 2 (NCT03986138) was conducted in adults with suspected enhancing abnormalities in at least one body region head and neck, thorax, abdomen, pelvis, and musculoskeletal system. In both studies, patients received Elucirem 0.05 mmol/kg and gadobutrol 0.1 mmol/kg as an active comparator. These were administered in random order and separated by a time interval between two and 14 days. An MRI was performed before and after administration of each contrast agent. Readers were presented with batches of approximately 20 to 40 MRIs containing either pre-contrast or paired pre- and post-contrast images in random order. Readers (neuroradiologists or radiologists with expertise in interpretation of brain and spine MRI) scored up to three lesions for border delineation, internal morphology, and contrast enhancement, each on a scale from 1 to 4; each patient served as their own control. The total number of lesions was also reported. An additional independent central reader performed lesion tracking to allow matching of lesions between pre-contrast and paired images.

The primary endpoint analysis for both supportive clinical studies compared average score for matching lesions three visualization parameters between pre-contrast and paired image sets. The primary objective was to determine whether paired pre- and post-contrast imaging with Elucirem is superior to pre-contrast imaging in terms of the three visualization parameters. Analyses for this objective included patients in the full analysis set (FAS). The null hypothesis was that the difference in mean scores between paired and pre-contrast images for each co-primary endpoint was 0, and the alternate hypothesis was that this difference was greater than 0. Significance was tested at α=0.025. The null hypothesis had to be rejected for all three parameters (co-primary endpoints) for a reader to be successful, and at least two out of three readers had to be successful.

In Study 1 conducted in patients with CNS lesions, three blinded readers' evaluations demonstrated superiority of the combined unenhanced/contrast-enhanced MRI with Elucirem over unenhanced MRI (Pre) for lesion visualization ($p<0.0001$ in all cases).[e] Table 2 displays the primary efficacy results.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

Table 2. [CNS, subject-level] Co-primary efficacy endpoints: off-site reading – MRI with Elucirem – paired vs pre – mixed model - FAS 1 (N = 239)

FAS 1 (N = 239)	n	LS Mean (SE)			95% CI difference	p-value
		Paired	Pre	Difference		
Border delineation						
Reader 1	227	3.90 (0.02)	2.08 (0.02)	1.82 (0.03)	(1.76, 1.88)	<.0001
Reader 2	229	3.64 (0.04)	1.74 (0.04)	1.90 (0.05)	(1.81, 2.00)	<.0001
Reader 3	202	3.97 (0.03)	2.61 (0.03)	1.36 (0.04)	(1.29, 1.44)	<.0001
Internal morphology						
Reader 1	227	3.92 (0.03)	1.66 (0.03)	2.26 (0.03)	(2.20, 2.33)	<.0001
Reader 2	229	3.65 (0.03)	1.88 (0.03)	1.77 (0.04)	(1.69, 1.85)	<.0001
Reader 3	202	3.97 (0.04)	1.96 (0.05)	1.96 (0.05)	(1.85, 2.06)	<.0001
Degree of contrast enhancement						
Reader 1	227	3.77 (0.03)	1.00 (0.03)	2.77 (0.04)	(2.69, 2.85)	<.0001
Reader 2	229	3.58 (0.03)	1.00 (0.03)	2.58 (0.05)	(2.49, 2.67)	<.0001
Reader 3	202	3.90 (0.02)	1.00 (0.02)	2.90 (0.03)	(2.84, 2.95)	<.0001

Abbreviations: FAS: Full analysis set; CI: Confidence Interval; LS: Least Squares; SE: Standard Error.
Source: FDA Unireview for Elucirem, Review in progress. Accessed Sept 13 2022, Table 11-1 on page 83/150 of GDX-44-010 Study Report: report-body-4-21-00161.pdf confirmed by the FDA statistical reviewer analysis.

In Study 2 conducted in patients with lesions outside the CNS, three blinded readers' evaluations demonstrated superiority of the combined unenhanced/contrast-enhanced MRI with Elucirem over unenhanced MRI (Pre) for lesion visualization (p<0.0001 in all cases). Table 3 displays the primary efficacy results.

Table 3. [Outside CNS, subject-level] Co-primary efficacy endpoints: off-site reading – MRI with Elucirem – paired vs pre – mixed model – FAS 1 (N = 278)

FAS 1 (N = 278)	n	LS Mean (SE)			95% CI difference	p-value
		Paired	Pre	Difference		
Border delineation						
Reader 1	251	3.79 (0.03)	2.26 (0.03)	1.53 (0.04)	(1.46, 1.60)	<.0001
Reader 2	230	3.48 (0.06)	3.01 (0.06)	0.47 (0.06)	(0.36, 0.58)	<.0001
Reader 3	262	3.49 (0.03)	1.78 (0.03)	1.71 (0.04)	(1.65, 1.78)	<.0001
Internal morphology						
Reader 1	251	3.80 (0.02)	1.99 (0.02)	1.81 (0.03)	(1.76, 1.87)	<.0001
Reader 2	230	3.75 (0.05)	3.22 (0.05)	0.53 (0.06)	(0.42, 0.64)	<.0001
Reader 3	262	3.72 (0.03)	1.69 (0.03)	2.03 (0.04)	(1.95, 2.11)	<.0001
Degree of contrast enhancement						
Reader 1	251	3.64 (0.03)	1.00 (0.03)	2.64 (0.04)	(2.56, 2.72)	<.0001
Reader 2	230	3.82 (0.05)	1.00 (0.05)	1.82 (0.07)	(1.68, 1.96)	<.0001

Reader 3	262	3.33 (0.03)	1.00 (0.03)	2.33 (0.04)	(2.26, 2.41)	<.0001

Abbreviations: CI: Confidence Interval; H&N: head and neck; LS: Least Squares; MSK: musculoskeletal; SE: Standard Error.
Source: FDA Unireview for Elucirem, Review in progress. Accessed Sept 13 2022--Table 11-1 on page 83/150 of GDX-44-010 Study Report: report-body-4-21-00161.pdf confirmed by the FDA statistical reviewer analysis

5 Risk Assessment & Safe-Use Conditions

The review team evaluated a pooled safety set of 1047 patients that included patients from eight clinical studies who received at least one dose of Elucirem. Overall there were no unexpected safety concerns identified by the review team. The most common adverse reactions were headache, nausea, and various injection site related events. These are all listed as adverse reactions in the approved labeling for multiple GBCAs, and the reported incidence of these events in the Elucirem clinical program was of a similar magnitude.

5.1 Death and Serious Adverse Events

There were two deaths in the clinical program and only one was a patient that had been administered Elucirem, the other occurred in a patient that had not yet been administered any contrast agent. The death in the patient that have been given Elucirem occurred more than 20 days after administration and well after Elucirem would be expected to be excreted; the clinical team does not attribute this death to the study drug.

A total of 17 serious adverse events (SAEs) were reported in 12 patients (1.1% of the safety population) after administration of Elucirem; this includes the one death after administration discussed above. The clinical review team concluded that one SAE was related to the study drug. A patient had an elevation in blood creatinine. No associated symptoms were reported, no treatment was needed and the serum creatinine decreased to normal levels by 20 days post-injection. The event was considered serious due to investigator assessment of medical importance. The event also met a protocol-defined subject stopping rule of increase in serum creatinine so it led to discontinuation from the study. The review team considered that that the event was related to Elucirem treatment but noted that the absolute change in creatinine was small. The remaining SAEs were considered unrelated to Elucirem by the investigators and the Applicant.[f]

5.2 Adverse Events of Special Interest

The association between GBCAs and nephrogenic systemic fibrosis (NSF), a rare, serious, potentially fatal disease, has been reported in patients with acute kidney injury (AKI) or severe chronic kidney disease (CKD). The impaired renal clearance in these patients causes increased levels of the GBCAs, which are retained longer in the body. There is a box warning for the class of GBCAs for NSF. In general, for all patients, a lower dose of gadolinium in general is preferred due to risk of NSF and retention of gadolinium in normal tissues. For this reason, the Applicant selected 0.05 mmol/kg Elucirem as the recommended dose since it is half the gadolinium dose compared to other GBCAs approved for similar indications. No suspected NSF or NSF-related symptoms

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

were reported in any study in the clinical program, including during the long term three and six month follow ups.

Other AE of special interests included events of torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope (excluding vasovagal reaction due to blood sampling), seizures and increase in serum creatinine. Other than the elevation of serum creatinine discussed above in the SAE section, none of the events were seen in the clinical program.

6 Expected Post Market Use

MRIs are used to image organs and tissues in the body for diagnostic purposes. After a physician orders the MRI, patients can have their MRI done at hospitals or outpatients radiology centers; therefore, Elucirem would be administered in radiology suites and departments in healthcare facilities that perform MRI.

7 Proposed Risk Management Activities

The Applicant did not propose any risk management activities for Elucirem beyond routine pharmacovigilance and labeling.

The Agency is planning to request a post-market study to evaluate the effects of Elucirem on neurobehavioral testing over repeated administration. Free gadolinium is considered toxic at doses necessary for MRI and we have learned that there is potential for gadolinium to be retained tissues after administration of a GBCA.[5] The post market prospective longitudinal cohort trial will evaluate the effects of repetitive Elucirem administration on a neurobehavioral testing over the course of at least five administrations. The Agency will also require a deferred pediatric study under the Pediatric Research Equity Act in patients aged 0 to 2 years.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Elucirem on the basis of the efficacy and safety information currently available. The safety concerns associated with Elucirem are NSF, hypersensitivity reactions, gadolinium retention, acute kidney injury, extravasation and injection site reactions, and interference with visualization of lesions visible with non-contrast MRI. These safety concerns are well known class wide risks and will be communicated in product labeling. As discussed in Section 5, there were no new signals or unexpected events identified in the Elucirem clinical program compared to other GBCA products. As a result, GBCA class labeling will be sufficient and a REMS is not necessary. The labeling will include a Box Warning for NSF and a Medication Guide to communicate important safety information and the class wide safety risks to patients.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Elucirem to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and

labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should the Division of Imaging and Radiation Medicine have any concerns or questions, or if new safety information becomes available, please send a consult to DRM.

10 References

[1] *MRI* downloaded from https://www.mayoclinic.org/tests-procedures/mri/about/pac-20384768, accessed 9/19/2022.

[2] Crues J, Bydder G. Frontiers in musculoskeletal imaging. *J Magn Reson Imaging* 2007;25:232–3

[3] *Magnetic Resonance Imaging* Downloaded from https://www.nibib.nih.gov/science-education/science-topics/magnetic-resonance-imaging-mri, accessed 9/19/2022.

[4] *MRI and Information on Gadolinium-Based Contrast Agents* Downloaded from https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-gadolinium-based-contrast-agents, accessed 9/19/2022.

[5] Lancelot E, Raynaud JS, Desché P. Current and Future MR Contrast Agents: Seeking a Better Chemical Stability and Relaxivity for Optimal Safety and Efficacy. Invest Radiol. 2020;55(9):578-588.

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