NEW DRUG APPROVAL

Brand Name	Elucirem™
Generic Name	gadopiclenol
Drug Manufacturer	Liebel-Flarsheim Company LLC

New Drug Approval

FDA approval date: September 21, 2022

Review designation: Priority

Type of review: Type 1 - New Molecular Entity and Type 4 - New Combination; New Drug Application (NDA): 216986

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Contrast agents are pharmaceuticals that increase the information content of diagnostic images. They serve to improve the sensitivity and specificity of diagnostic images by altering the intrinsic properties of tissues, which influence the fundamental mechanisms of contrast. Strategic localization of the agent can regionally change the tissue properties and result in preferential enhancement. MRI is unique among diagnostic modalities because it uses more than one intrinsic property of the tissue being imaged. All other diagnostic imaging modalities depend on one inherent tissue property for image formation. Gadolinium-based contrast agent concentration in a certain tissue depends on the pharmacokinetics of the contrast agent, the structure of an agent, charge on the structure of an agent, magnetic field strength, tissue and organs' environment, and organ and tissue architecture. In vitro, the contrast agent concentration is linearly related to relaxivity (R). In vivo, however, this is limited by additional relaxation effects. Gadolinium-based contrast agents are paramagnetic, that is, these atoms act like ferromagnetic and superparamagnetic substances, and have a positive magnetic susceptibility. The effect of paramagnetic substances is several orders of magnitude weaker than that of other substances with positive susceptibility. Paramagnetic atoms have independent magnetically diffused moments.

Epidemiology: It is estimated that approximately 50 million doses of gadolinium-based contrast media (GBCM; also known as gadolinium-based contrast agents or GBCAs) are injected annually, and that since 1988 more than 500 million doses have been administered worldwide, comprising approximately one-third of MRI examinations. While GBCM-enhanced MRI examinations are preferred over unenhanced examinations for many indications, they may be delayed or denied in patients with impaired kidney function due to concerns of adverse events, including nephrogenic systemic fibrosis (NSF) and nephrotoxicity. However, recommendations about the use of GBCM in patients with kidney disease have evolved and have been inconsistent in clinical practice among radiologists and nephrologists, even within the same institution.

Efficacy

The safety and effectiveness of Elucirem™ for lesion visualization were evaluated in two prospective, double blind, randomized, crossover clinical studies. Study 1 (NCT03996447) was performed in adults with known or highly suspected CNS lesions with focal areas of disruption of the blood-brain barrier. Study 2 (NCT03986138) was performed in adults with suspected enhancing abnormalities in at least one body region among the head and neck, thorax, abdomen, pelvis, and musculoskeletal system.

In each study, patients received both Elucirem™ 0.05 mmol/kg and gadobutrol 0.1 mmol/kg (as an active comparator) in random order separated by 2 days to 14 days. Magnetic resonance imaging was performed before and after administration of each contrast agent.

Pre-contrast and paired (consisting of both pre-contrast and post-contrast images for the same drug) image sets were independently evaluated by three central readers who were blinded to identity of the contrast agent. Readers scored up to three lesions per patient for border delineation, internal morphology, and contrast enhancement, each on a scale from 1 to 4. 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 analysis compared the patient-level average score for matching lesions for each visualization parameter between pre-contrast and paired image sets.

Visualization of CNS Lesions: Study 1 included 256 patients with known or highly suspected CNS lesion(s). Among the enrolled patients, 239 had assessable pre-contrast and paired images with at least one matching lesion for at least one reader. These patients had a mean age of 57 years (range: 18 years to 84 years), 52% were female, and 83% were White.

All three blinded readers' evaluations of paired pre-contrast plus post-contrast images and pre-contrast images alone for all lesion visualization criteria, the pre-specified co-primary efficacy endpoints, are presented in Table 1.

Table 1. Patient-Level CNS Lesion Visualization Scores by Reader, Paired vs. Pre-contrast in Patients Receiving Elucirem™ 0.05 mmol/kg Intravenously

LS Mean (SE)					
	n	**Paired**	**Pre-contrast**	**Difference***	**95% CI Difference**
Border delineation					
Reader 1	227	3.90 (0.02)	2.08 (0.02)	1.82 (0.03)	(1.76, 1.88)
Reader 2	229	3.64 (0.04	1.74 (0.04)	1.90 (0.05)	(1.81, 2.00)
Reader 3	202	3.97 (0.03)	2.61 (0.03)	1.36 (0.04)	(1.29, 1.44)
Internal morphology					
Reader 1	227	3.92 (0.03)	1.66 (0.03)	2.26 (0.03)	(2.20, 2.33)
Reader 2	229	3.65 (0.03)	1.88 (0.03)	1.77 (0.04)	(1.69, 1.85)
Reader 3	202	3.97 (0.04)	2.01 (0.04)	1.96 (0.05)	(1.85, 2.06)
Degree of contrast enhancement					
Reader 1	227	3.77 (0.03)	1.00 (0.03)	2.77 (0.04)	(2.69, 2.85)
Reader 2	229	3.58 (0.03)	1.00 (0.03)	2.58 (0.05)	(2.49, 2.67)
Reader 3	202	3.90 (0.02)	1.00 (0.02)	2.90 (0.03)	(2.84, 2.95)

LS: Least Squares; SE: Standard Error; CI: Confidence Interval.

Only matching lesions are considered. The mixed models based on the full analysis set (N=239) include lesion visualization factor as dependent variable, MRI modality (Pre-contrast and Paired MRI) as fixed f actors, and patient as a random factor. *$p < 0.0001$ for all rows.

Gadopiclenol lesion visualization scores and number of lesions identified per patient were similar to those for gadobutrol.

Visualization of Body Lesions: Study 2 included 304 patients presenting with known or suspected enhancing abnormality(ies) and/or lesion(s) in at least one region among the head and neck, musculoskeletal system including extremities, and body including thorax, abdomen, and pelvis. Among the enrolled patients, 278 had assessable pre-contrast and paired images with at least one matching lesion for at least one reader. These patients had a mean age of 57 years (range: 21 years to 86 years), 59% were female, and 71% were White.

Three readers assessed images of the head and neck, three other readers assessed images of the musculoskeletal system, and another three readers assessed other areas collectively referred to as the body (thorax, abdomen, and pelvis). Lesion visualization scores by reader in each anatomic region at patient-level as supportive analyses are summarized in Table 2.

Table 2. Patient-Level Body Lesion Visualization Scores by Reader and Anatomic Region, paired vs. Pre-contrast in Patients Receiving Elucirem™ 0.05 mmol/kg Intravenously

LS Mean (SE)

	n	Paired	Pre-contrast	Difference	95% CI difference
Head & Neck					
Border delineation					
Reader 1	15	3.71 (0.10)	2.13 (0.10)	1.58 (0.14)	(1.30, 1.86)
Reader 2	19	3.53 (0.18)	2.11 (0.18)	1.42 (0.18)	(1.06, 1.78)
Reader 3	13	3.92 (0.13)	2.85 (0.13)	1.08 (0.13)	(0.82, 1.33)
Internal morphology					
Reader 1	15	3.80 (0.07)	1.87 (0.07)	1.93 (0.10)	(1.74, 2.12)
Reader 2	19	3.74 (0.14)	2.05 (0.14)	1.68 (0.16)	(1.37, 2.00)
Reader 3	13	3.92 (0.12)	2.54 (0.12)	1.38 (0.14)	(1.10, 1.67)
Degree of contrast enhancement					
Reader 1	15	3.60 (0.11)	1.00 (0.11)	2.60 (0.16)	(2.29, 2.91)
Reader 2	19	3.68 (0.16)	1.00 (0.16)	2.68 (0.22)	(2.22, 3.15)
Reader 3	13	3.92 (0.11)	1.00 (0.11)	2.92 (0.15)	(2.61, 3.24)
Musculoskeletal system (including extremities)					
Border delineation					
Reader 1	17	3.00 (0.10)	2.06 (0.10)	0.94 (0.13)	(0.68, 1.20)
Reader 2	17	2.68 (0.20)	2.44 (0.20)	0.24 (0.19)	(-0.15, 0.62)
Reader 3	21	2.81 (0.10)	2.05 (0.10)	0.76 (0.10)	(0.56, 0.96)
Internal morphology					

Reader 1	17	3.00 (0.07)	2.00 (0.07)	1.00 (0.09)	(0.82, 1.18)
Reader 2	17	3.94 (0.15)	2.35 (0.15)	1.59 (0.17)	(1.25, 1.92)
Reader 3	21	2.90 (0.09)	2.05 (0.09)	0.86 (0.11)	(0.64, 1.08)
Degree of contrast enhancement					
Reader 1	17	2.82 (0.10)	1.00 (0.10)	1.82 (0.15)	(1.53, 2.12)
Reader 2	17	3.33 (0.17)	1.00 (0.17)	2.33 (0.24)	(1.847, 2.82)
Reader 3	21	3.06 (0.08)	1.00 (0.08)	2.06 (0.12)	(1.82, 2.31)
Body (thorax, abdomen, pelvis)					
Border delineation					
Reader 1	219	3.86 (0.03)	2.28 (0.03)	1.57 (0.04)	(1.50, 1.64)
Reader 2	194	3.54 (0.06)	3.15 (0.06)	0.40 (0.06)	(0.29, 0.51)
Reader 3	228	3.53 (0.03)	1.69 (0.03)	1.84 (0.03)	(1.78, 1.90)
Internal morphology					
Reader 1	219	3.86 (0.02)	2.00 (0.02)	1.87 (0.03)	(1.82, 1.92)
Reader 2	194	3.74 (0.05)	3.41 (0.05)	0.33 (0.05)	(0.23, 0.43)
Reader 3	228	3.78 (0.03)	1.60 (0.03)	2.17 (0.03)	(2.11, 2.24)
Degree of contrast enhancement					
Reader 1	219	3.71 (0.03)	1.00 (0.03)	2.71 (0.04)	(2.63, 2.79)
Reader 2	194	2.69 (0.05)	1.00 (0.05)	1.69 (0.07)	(1.54, 1.83)
Reader 3	228	3.33 (0.03)	1.00 (0.03)	2.33 (0.44)	(2.25, 2.40)

LS: Least Squares; SE: Standard Error; CI: Confidence Interval.

Only matching lesions are considered. The mixed models based on the full analysis set (N=278) include lesion visualization factor as a dependent variable, patient as a random factor, and MRI modality (Pre-contrast and Paired MRI), body regions, and MRI body regions as fixed factors.

Gadopiclenol lesion visualization scores and number of lesions identified per patient were similar to those for gadobutrol.

Safety: Most common adverse reactions (incidence >0.2%) in patients are injection site pain, headache, nausea, injection site warmth and coldness, dizziness, and localized swelling.

Safety

ADVERSE EVENTS

Table 3 lists adverse reactions that occurred in > 0.2% of patients who received 0.05 mmol/kg Elucirem™.

Table 3. Adverse Reactions Reported in > 0.2% of Patients Receiving Elucirem™ in Clinical Trials	
Adverse Reaction	**Elucirem™ 0.05 mmol/kg (n=708) (%)**

Injection site pain	0.7
Headache	0.7
Nausea	0.4
Injection site warmth	0.4
Injection site coldness	0.3
Dizziness	0.3
Localized swelling	0.3

Adverse reactions that occurred with a frequency ≤ 0.2% in patients who received 0.05 mmol/kg Elucirem™ included: maculopapular rash, vomiting, worsened renal impairment, feeling hot, pyrexia, oral paresthesia, dysgeusia, diarrhea, pruritus, allergic dermatitis, erythema, injection site paresthesia, Cystatin C increase, and blood creatinine increase.

Adverse Reactions in Pediatric Patients: One study with a single dose of Elucirem™ (0.05 mmol/kg) was conducted in 80 pediatric patients aged 2 years to 17 years, including 60 patients who underwent a central nervous system (CNS) MRI and 20 patients who underwent a body MRI. One adverse reaction (maculopapular rash of moderate severity) in one patient (1.3%) was reported in the CNS cohort.

WARNINGS & PRECAUTIONS

Nephrogenic Systemic Fibrosis: Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73 m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30-59 mL/min/1.73 m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60-89 mL/min/1.73 m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs.

Hypersensitivity Reactions: With GBCAs, serious hypersensitivity reactions have occurred. In most cases, initial symptoms occurred within minutes of GBCA administration and resolved with prompt emergency treatment.

Gadolinium Retention: Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver, and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with gadodiamide causing greater retention than other linear agents such as gadoxetate disodium and gadobenate dimeglumine. Retention is lowest and similar among the macrocyclic GBCAs such as gadoterate meglumine, gadobutrol, gadoteridol, and gadopiclenol.

Acute Kidney Injury: In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent. Do not exceed the recommended dose.

Extravasation and Injection Site Reactions: Injection site reactions such as injection site pain have been reported in the clinical studies with Elucirem™. Extravasation during Elucirem™ administration may result in tissue irritation. Ensure catheter and venous patency before the injection of Elucirem™.

Interference with Visualization of Lesions Visible with Non-Contrast MRI: As with any GBCA, Elucirem™ may impair the visualization of lesions seen on non-contrast MRI. Therefore, caution should be exercised when Gadopiclenol MRI scans are interpreted without a companion non-contrast MRI scan.

CONTRAINDICATIONS

Contraindicated in patients with history of hypersensitivity reactions to Elucirem™.

Clinical Pharmacology

MECHANISMS OF ACTION

Gadopiclenol is a paramagnetic molecule (macrocyclic non-ionic complex of gadolinium) that develops a magnetic moment when placed in a magnetic field. The magnetic moment alters the relaxation rates of water protons in its vicinity in the body, leading to an increase in signal intensity (brightness) of tissues.

Dose & Administration

ADULTS

0.05 mmol/kg (0.1 mL/kg) intravenously at approximately 2 mL/sec.

PEDIATRICS

Refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 0.5mmol/mL of gadopiclenol in single-dose vials, single-dose prefilled syringes, and pharmacy bulk packages.