Guerbet Announces U.S. Food and Drug Administration (FDA) Approval of Elucirem™ (Gadopiclenol) Injection for Use in Contrast-Enhanced MRI

- Elucirem™ has the highest relaxivity compared to other non-specific GBCAs [1]
- Elucirem™ requires only half the gadolinium dose of conventional non-specific GBCAs
- Elucirem™ will be manufactured in Raleigh, North Carolina by Liebel-Flarsheim™ Company LLC, a Guerbet Group company.

Princeton, New Jersey, September 21, 2022 – Guerbet, a global leader in medical imaging with more than 30 years of experience in MRI, and the first to bring a macrocyclic GBCA to the global market, is proud to announce the U.S. Food and Drug Administration (FDA) has approved Elucirem™ (gadopiclenol) injection. This next generation, highly stable macrocyclic gadolinium-based contrast agent (GBCA), has the highest relaxivity in its class for magnetic resonance imaging (MRI) and is indicated for use in adults and children aged 2 years and older. [4] FDA granted Elucirem™ priority review, a designation assigned to applications for drugs that provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies.[5]

GBCAs improve the contrast between lesions and surrounding tissues by accelerating the relaxation of protons thanks to interaction with gadolinium atoms. Gadopiclenol, the active substance of Elucirem™, has been designed to enable twice as much interaction, resulting in the highest relaxivity among all non-specific GBCAs.[4] This allows use at half the conventional dose of other non-specific GBCAs.

Elucirem™ (Gadopiclenol) Injection is used to detect and visualize lesions with abnormal vascularity in the central nervous system (brain, spine and associated tissues), and the body (head and neck, thorax, abdomen, pelvis and musculoskeletal system).

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"*Guerbet is a leader in the field of GBCA-based MRI imaging agents and developed the first macrocyclic GBCA. We are extremely gratified that this approval from the FDA will make it possible for clinicians and patients to benefit from the innovations brought by Elucirem™*" said David Hale, Chief Executive Officer of Guerbet.

The approval was primarily based on data from two adequate and well-controlled Phase III studies completed in March 2021 which showed that gadopiclenol was designed to improve image quality in brain and body MRI at half the conventional gadolinium dose.[2,3] In both the PICTURE trial for CNS MRI and the PROMISE trial in Body MRI, gadopiclenol-enhanced MRI at 0.05 mmol/kg showed superiority as compared to unenhanced MRI and non-inferiority as compared to gadobutrol at 0.1 mmol/kg as assessed in 3 lesion visualization co-primary criteria: border delineation, internal morphology and contrast enhancement.[2,3] In the PICTURE trial, readers preferred the quality of visualization obtained with a half dose of Gadopiclenol compared to a full dose of Gadobutrol.[2]

Gadopiclenol was evaluated in 1,047 patients with doses ranging from 0.025 mmol/kg BW (one half the recommended dose) to 0.3 mmol/kg BW (six times the recommended dose). A total of 708 patients (age range two years to 88 years) received the recommended dose of 0.05 mmol/kg BW. No major safety signals were reported during the development of gadopiclenol, and the adverse reactions reported during the two-Phase III studies were similar for both products administered. The most common adverse reactions (incidence >0.2%) in patients who received Gadopiclenol were injection site pain, headache, nausea, injection site warmth and coldness, dizziness, and localized swelling.

"After 15 years of dedicated research to bring Elucirem to fruition Guerbet is *very proud of this FDA approval of Elucirem™, confirming the commitment of Guerbet's R&D teams in developing solutions for MRI, adapted to the needs of radiologists and patients*." said Dr Philippe Bourrinet, Senior Vice-President Development, Medical & Regulatory Affairs of Guerbet.

Elucirem™ will be available in glass vials, pharmacy bulk package and plastic pre-filled syringes which can help to streamline workflow in the imaging suite. It will be manufactured by Liebel-Flarsheim™ Company LLC, a Guerbet Group company, in Raleigh, North Carolina.

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About Guerbet

At Guerbet, we build lasting relationships so that we enable people to live better. That is purpose. We are a global leader in medical imaging, offering a comprehensive range pharmaceutical products, medical devices, and digital and AI solutions for diagnostic interventional imaging. As pioneers in contrast products for 95 years, with more than 2, employees worldwide, we continuously innovate and devote 8%-10% of our revenue to resea and development in five centers in France, Israel, and the United States. Guerbet (GBT) is lis on Euronext Paris (segment B – mid caps) and generated €732 million in revenue in 2021. For m information, please visit visit www.guerbet.com.

About Gadopiclenol

Gadopiclenol, initially invented by Guerbet with subsequent contribution of Bracco intellectual property, is a new macrocyclic gadolinium-based contrast agent (GBCA) with high relaxivity. The efficacy and safety of Gadopiclenol have been evaluated in MRI of the Central Nervous System, head and neck, thorax, breast, abdomen, pelvis and musculoskeletal system (refer to the approved USPI for full information). Details on Phase III clinical trials are available on www.ClinicalTrials.gov:

- *Efficacy and Safety of Gadopiclenol for Central Nervous System (CNS) Magnetic Resonance Imaging (MRI) Full Text View - ClinicalTrials.gov*
- *Efficacy and Safety of Gadopiclenol for Body Magnetic Resonance Imaging (MRI) Full Text View -gov*

The Guerbet and Bracco Imaging Collaboration

Guerbet and Bracco Imaging entered in December 2021 into a worldwide collaboration on Gadopiclenol manufacturing and research and development activities. Gadopiclenol will be commercialized independently under separate brands. Both Guerbet and Bracco Imaging each own valuable intellectual property on gadopiclenol. Furthermore, after an agreed transition period when Guerbet manufactures gadopiclenol for both Guerbet and Bracco Imaging, both companies will manufacture gadopiclenol active ingredient and finished product.

Forward-looking statements

This press release may contain statements of a forward-looking nature, based on assumptions and predictions made by the management of the Guerbet group. Various known and unknown risks, uncertainties and other factors could lead to marked

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differences between the future results, financial situation, development and performances of the company, and the estimates made here. These factors include those mentioned in

the public reports of Guerbet, available on its website www.guerbet.com. The company assumes no responsibility whatsoever in relation to the updating of these forward-looking statements, or how they correspond to future events or developments.

ELUCIREM™ (gadopiclenol) injection Important Safety Information

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
See full prescribing information for complete boxed warning

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.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR <30 mL/min/1.73 m^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 (for example, age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**

Indications and Usage
ELUCIREM™ (gadopiclenol) injection is indicated in adult and pediatric patients aged 2 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), and the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system).

Contraindications
History of hypersensitivity reactions to ELUCIREM

Warnings and Precautions

- **Nephrogenic Systemic Fibrosis:** GBCAs increase the risk for 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 as well as patients with acute kidney injury.
- **Hypersensitivity Reactions:** With GBCAs, serious hypersensitivity reactions have occurred. In most cases, initial symptoms occurred within minutes of GBCA

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administration and resolved with prompt emergency treatment. Before ELUCIREM administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to ELUCIREM.

- **Gadolinium Retention:** Gadolinium is retained for months or years in several organs. Linear GBCAs cause more retention than macrocyclic GBCAs. Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function. While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible
- **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.

Adverse Reactions:
In clinical trials, the most frequent adverse reactions that occurred in > 0.2% of patients who received ELUCIREM included: injection site pain, headache, nausea, injection site warmth, injection site coldness, dizziness, and localized swelling Adverse reactions that occurred with a frequency ≤ 0.2% in patients who received 0.05 mmol/kg BW 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.

Use in Specific Populations

- **Pregnancy:** GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. There are no available data on ELUCIREM use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

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- **Lactation:** There are no data on the presence of ELUCIREM in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in breast milk.
- **Pediatric Use:** The safety and effectiveness of ELUCIREM have not been established in pediatric patients younger than 2 years of age.
- **Geriatric Use:** This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function.
- **Renal Impairment:** In patients with renal impairment, the exposure of gadopiclenol is increased compared to patients with normal renal function. This may increase the risk of adverse reactions such as nephrogenic systemic fibrosis (NSF). Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. No dose adjustment of ELUCIREM is recommended for patients with renal impairment. ELUCIREM can be removed from the body by hemodialysis

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see the full Prescribing Information, including the patient Medication Guide, for additional important safety information.

1. *Elucirem [package insert]. Princeton, NJ: Guerbet LLC; 2022*
2. *Data on file (PICTURE trial. GDX-44-010)*
3. *Data on file (PROMISE trial. GDX-44-011)*
4. *Robic, C., Port, M., Rousseaux, O., Louguet, S., Fretellier, N., Catoen, S., Factor, C., Le Greneur, S., Medina, C., Bourrinet, P., Raynal, I., Idée, J. M., & Corot, C. (2019). Physicochemical and Pharmacokinetic Profiles of Gadopiclenol: A New Macrocyclic Gadolinium Chelate With High T1 Relaxivity. Investigative radiology, 54(8), 475–484. https://doi.org/10.1097/RLI.0000000000000563*
5. US FDA. Priority Review. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review. Accessed August 22, 2022.

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