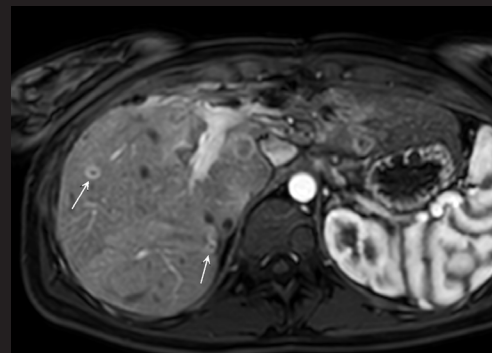
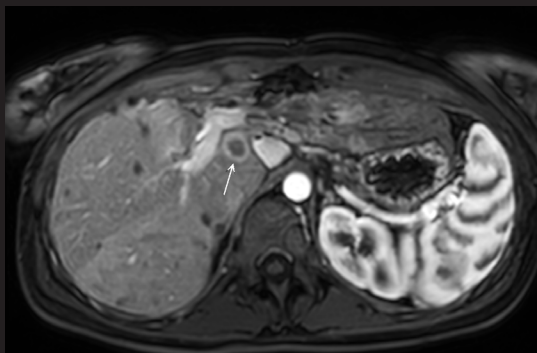
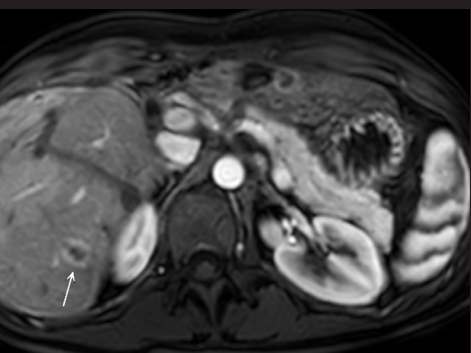


Clinical Applications in MRI: Managing Patient Outcomes

Max Wintermark, MD, MS, MBA



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Introduction

Gadolinium-based contrast agents (GBCAs) are indispensable to MR imaging, as they enhance patient care through detailed visualization of tissue and vascular abnormalities.¹ GBCAs have faced two areas of concern over the last 20 years.² The first is nephrogenic systemic fibrosis (NSF) in patients with severe renal insufficiency, the incidence of which has been near zero in recent years through the implementation of risk mitigation strategies.² The second is gadolinium retention in body tissues, which, while leading to regulatory actions around the world, still lacks evidence of any clinical consequence.²

The urgent need for a GBCA that reduces unnecessary gadolinium exposure without compromising diagnostic efficacy has driven the development of new options that improve upon the physicochemical properties of older agents. As the most recently approved GBCA, gadopipiclenol has captured significant interest because of its high kinetic stability and relaxivity compared with standard GBCAs; these characteristics together

allow for administration of a lower gadolinium dose without compromising contrast enhancement.³⁻⁷ This article discusses considerations for using gadopipiclenol to improve patient care.

The Rationale for Gadopipiclenol Use

Balancing the risks and benefits of GBCA administration prior to MRI examination is crucial, particularly for patients who may require repeated examinations over time. These include children, women at high risk for breast cancer who must undergo periodic screening, and patients with chronic conditions that necessitate ongoing monitoring, such as multiple sclerosis.^{5,8} In all cases, best practices from the American College of Radiology (ACR) dictate the administration of the lowest GBCA dose needed to obtain adequate diagnostic information.² Therefore, selecting the GBCA that can best answer the clinical question is critical.

Every GBCA contains a gadolinium (Gd^{3+}) ion bound to a ligand that influences the agent's overall kinetic stability and relaxivity.² Gadopipiclenol was designed to optimize Gd^{3+} ion

access to water molecules, resulting in an $r1$ relaxivity up to three times higher than that of other GBCAs in water and serum and at all field strengths.³ A high $r1$ relaxivity is important, as it improves the contrast between abnormal lesions and surrounding tissues, which can aid diagnosis and treatment planning.³ Phase 3 clinical studies have shown that at the approved dose of 0.05 mmol/kg, gadopipiclenol offers similar diagnostic performance to a standard GBCA administered at 0.1 mmol/kg while maintaining a strong safety profile.^{4,5}

A key property of GBCAs is kinetic stability, with macrocyclic agents being more stable than linear agents, owing to the former's cage-like configuration that allows for tighter binding of the Gd^{3+} ion.⁹ While all GBCAs are linked to some degree of gadolinium retention, the higher stability of macrocyclic agents results in lower potential for Gd^{3+} ion dissociation, reducing the risk of NSF development and gadolinium retention in tissues.¹⁰ In studies conducted in rat models, gadopipiclenol has been associated with lower gadolinium tissue retention compared to linear GBCAs.^{11,12}

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Disclosures: Dr Wintermark is an advisory board member for Subtle Medical, Magnetic Insight, and Icometrix.

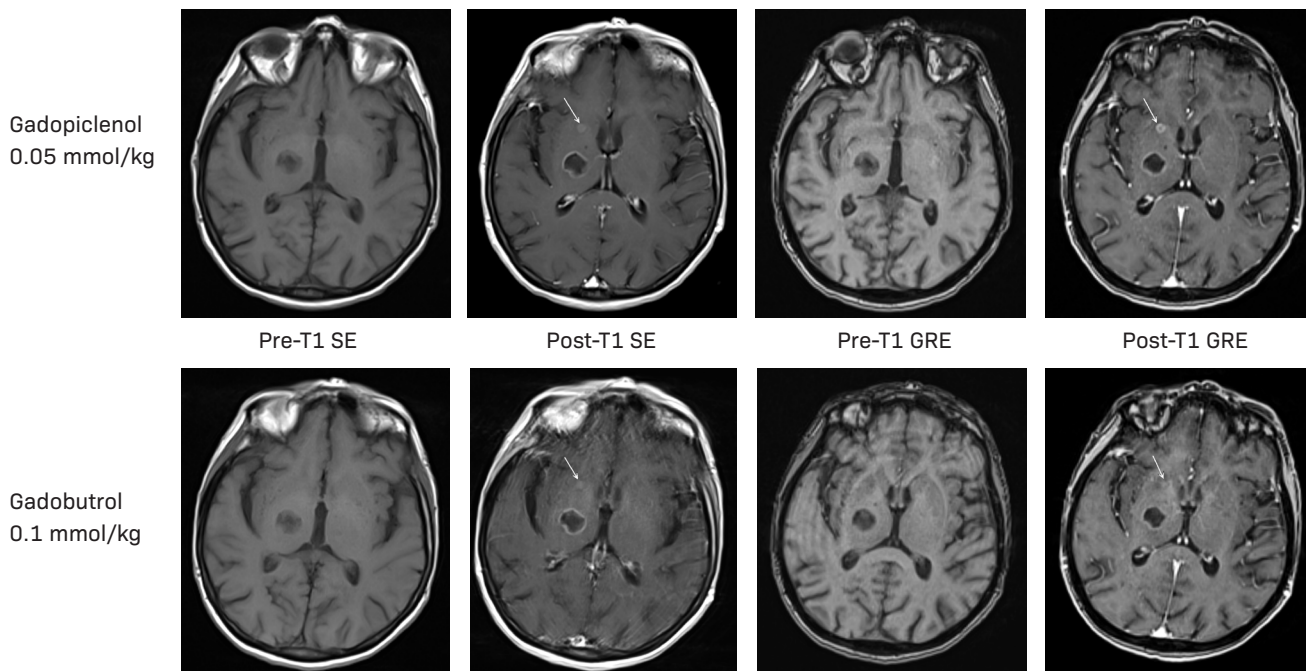


Figure 1. A 66-year-old male with brain metastases from unknown primary cancer.¹⁹ The metastasis in the right basal ganglia (arrow) is more conspicuous with 0.05 mmol/kg of gadopicholol compared to 0.1 mmol/kg of gadobutrol.

Furthermore, at its approved clinical dose of 0.05 mmol/kg, gadopicholol results in less gadolinium retention than the standard 0.1 mmol/kg dose of gadobutrol, indicating that retention is dose dependent.¹³ The ability to deliver a lower gadolinium dose without sacrificing diagnostic quality makes gadopicholol a highly desirable option among GBCAs.²

Compelling Clinical Research

A large body of evidence generated over the past few decades via randomized controlled trials confirms that a high-relaxivity agent can lead to better lesion detection and provide more diagnostic information than a standard-relaxivity agent when administered at the same dose for imaging the central nervous system (CNS).^{14–18} A similar evaluation was conducted in the phase 3 PICTURE study, which compared a 0.05 mmol/kg dose

of gadopicholol to 0.1 mmol/kg of gadobutrol.⁴ The primary endpoint, lesion visualization based on border delineation, internal morphology, and contrast enhancement, was assessed by three off-site, blinded readers. A 0.05 mmol/kg dose of gadopicholol was found to be noninferior to 0.1 mmol/kg of gadobutrol for all evaluated parameters across all readers.⁴ Gadopicholol also demonstrated a significantly higher enhancement percentage and lesion-to-background ratio across all readers. Two of the three readers found the contrast-to-noise ratio to be significantly higher with gadopicholol; they all preferred the gadopicholol-enhanced images in nearly half of the evaluations.⁴ The case of a 66-year-old subject with brain metastases from unknown primary cancer enrolled in the PICTURE study is shown in **Figure 1**.

Gadopicholol has also been studied in contrast-enhanced body MRI.

The phase 3 study, PROMISE, found a 0.05 mmol/kg dose of gadopicholol comparable to 0.1 mmol/kg of gadobutrol in 272 adults with at least one suspected focal lesion in one of three different body regions (head and neck; breast, thorax, abdomen, and pelvis; and the musculoskeletal system).⁵ Gadopicholol was shown to be noninferior to gadobutrol for all qualitative visualization parameters and across all readers. Readers also indicated no significant difference in preference between gadopicholol- and gadobutrol-enhanced images for most patients. Case examples of a 61-year-old male with cholangiocarcinoma (**Figure 2**) and a 51-year-old female with right breast cancer (**Figure 3**) show that contrast-enhanced MRI scans obtained with gadopicholol are similar to those obtained with gadobutrol. In both studies, a half gadolinium dose of gadopicholol was comparable to a full gadolinium dose with gadobutrol in terms of the

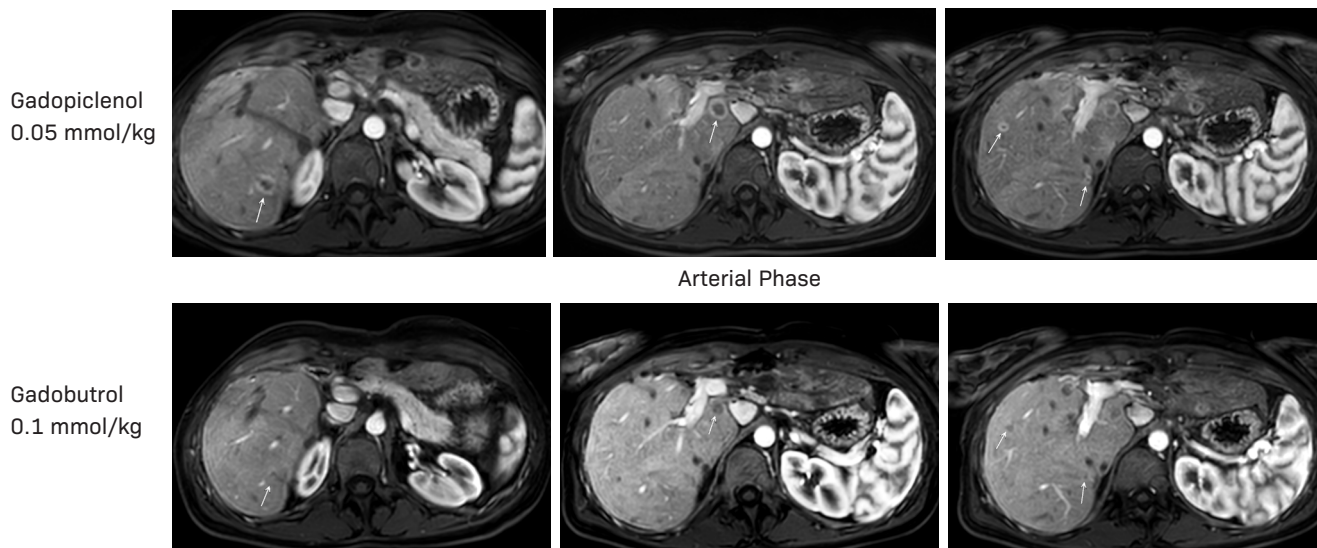


Figure 2. A 31-year-old female with cholangiocellular carcinoma. Images acquired in arterial phase show a much better detection and delineation of multiple malignant nodules with gadopicholol at the dose of 0.05 mmol/kg (7 mL) than with gadobutrol at the dose of 0.1 mmol/kg (7 mL). A number of small lesions with gadopicholol show the most common pattern of cholangiocellular carcinoma, which is a thin peripheral rim of enhancement in arterial phase. This finding is not seen in most lesions after gadobutrol injection.²⁰

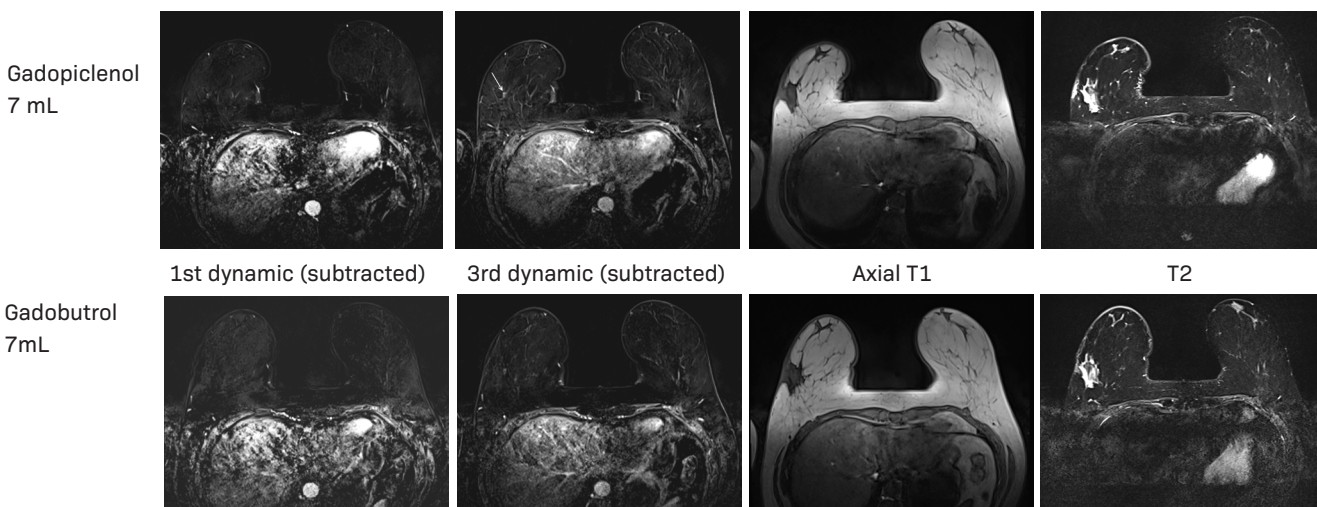


Figure 3. A 51-year-old female with right breast cancer. 7 mL of gadopicholol and 7 mL gadobutrol, given 7 days apart (gadopicholol first). Imaged via Siemens 3.0T.²⁰

degree of contrast enhancement and quality of morphologic lesion characteristics.^{4,5}

Impact of Gadopicholol on Patient Care

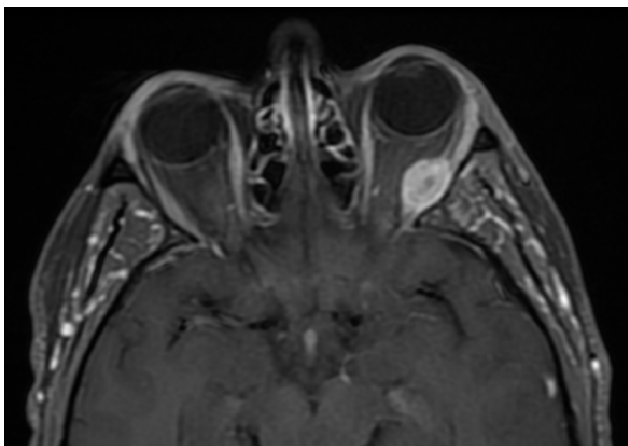
At The University of Texas MD Anderson Cancer Center, we see very sick patients who often travel long distances for oncologic imaging and treatment. As we consider

the types of patients and their imaging needs, we have found great value in incorporating gadopicholol into our workflow.

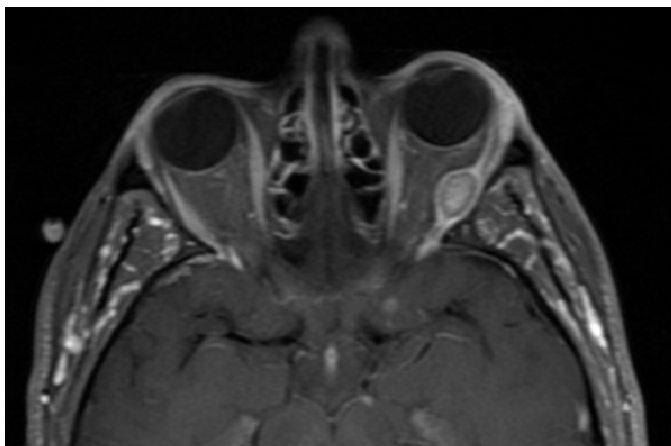
By using an agent that provides twice the r1 relaxivity of standard MRI contrast agents but at half the amount of gadolinium required for optimal imaging, we can improve patient care by detecting small lesions that may not demonstrate significant contrast with the surrounding

normal brain tissue or assess their size and number, while minimizing gadolinium exposure (**Figures 4 and 5**). This is particularly meaningful in vulnerable patient populations such as those who require repeated MRI examinations.

We have also observed another noteworthy benefit with gadopicholol in patients who require scanning of multiple body regions: same-day imaging. Historically, MRI acquisition

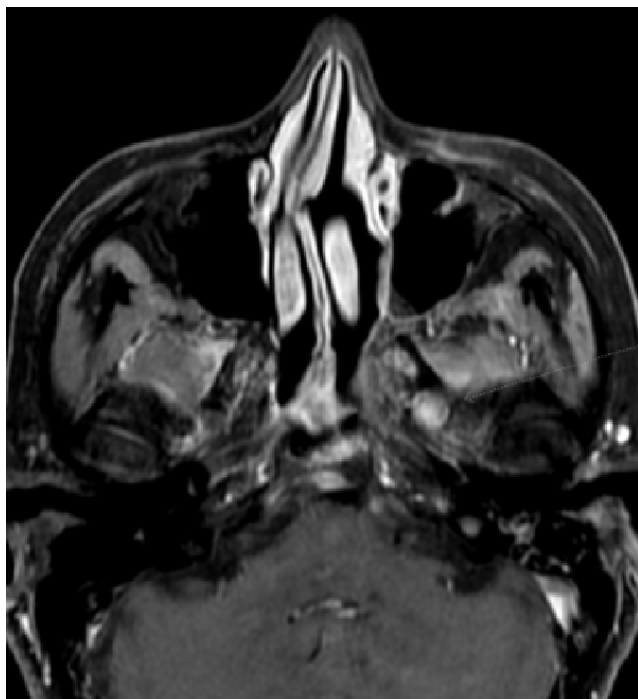


Gadopicle-nol 0.05 mmol/kg

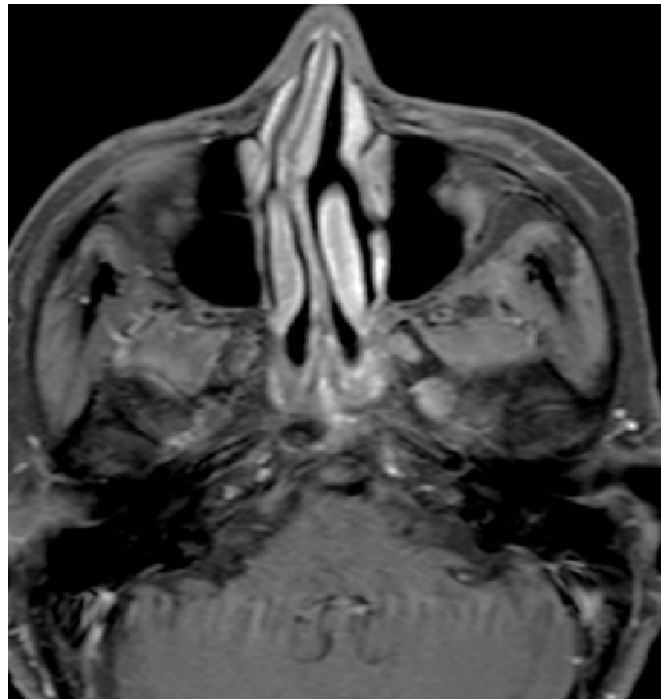


Gadobenate dimeglumine 0.1 mmol/kg

Figure 4. 33-year-old female with a history of small cell lung cancer. MRI of the orbits shows a metastasis in the lateral rectus muscle of the left orbit, enhancing more with 0.05 mmol/kg of gadopicle-nol compared to 0.1 mmol/kg of gadobenate dimeglumine.



Gadopicle-nol 0.05 mmol/kg



Gadobenate dimeglumine 0.1 mmol/kg

Figure 5. 60-year-old female with a history of adenoid cystic carcinoma of the left hard palate. MRI of the skull base shows perineural spread extending into the left foramen ovale, visualized slightly better with 0.05 mmol/kg of gadopicle-nol compared to 0.1 mmol/kg of gadobenate dimeglumine.

limitations associated with standard GBCAs meant that multiple body regions had to be scanned over successive days using multiple doses of GBCAs. For instance, when a patient is referred for an MRI of the abdomen and an MRI of the brain, these two MRI studies would typically be performed on two consecutive

days, each of them requiring the injection of a 0.1 mmol/kg dose of a standard GBCA, for a total of 0.2 mmol/kg. However, with gadopicle-nol we can perform both scans in one day. In our example, the MRI of the abdomen is performed first with a 0.05 mmol/kg dose of gadopicle-nol, after which the patient is

quickly repositioned in a head coil to obtain a postcontrast MRI of the brain without reinjecting contrast. This reduces the time to diagnosis and improves overall patient management and workflow. Patients no longer need to travel for multiple visits or extend their stay near our center to accommodate multi-day

imaging appointments. The peace of mind that comes from knowing their test results on the same day, moreover, positively impacts our patients' well-being. There is also an incremental benefit in terms of gadolinium exposure, with only a quarter of the total dose needed for multiple exams with gadopixelol versus that of a standard GBCA (ie, 0.05 mmol/kg of gadopixelol vs 0.2 mmol/kg or more of a standard GBCA). This means lower cumulative doses over the course of a patient's lifetime, especially for those who require long-term follow-up.

Summary

GBCAs improve the diagnostic value of MRI examinations across a wide range of medical conditions. By enhancing tissue contrast for more accurate diagnosis, careful disease monitoring, and improved treatment planning, gadopixelol represents a critical advance in contrast-enhanced MRI. As highlighted in the case examples discussed in this publication, gadopixelol has proved invaluable in managing complex conditions such as brain metastases, abdominal pathologies, and many others. While all GBCAs, including gadopixelol, are not without risk, their benefits in improving patient care are irrefutable. By understanding the behavior and safety profile of gadopixelol, radiologists can anticipate broad use of the agent to improve diagnostic accuracy and, ultimately, to deliver better patient care.

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VUEWAY® (gadopiclesol) solution for injection

Indications

VUEWAY injection is indicated in adults and children 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),
- the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system).

IMPORTANT SAFETY INFORMATION

WARNING: RISK ASSOCIATED WITH INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS

Risk Associated with Intrathecal Use

Intrathecal administration of gadolinium-based contrast agents (GBCAs) can cause serious adverse reactions including death, coma, encephalopathy, and seizures. VUEWAY is not approved for intrathecal use.

NEPHROGENIC SYSTEMIC FIBROSIS

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-contrast 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/1.73 m²), 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, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended VUEWAY dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.**

Contraindications

VUEWAY injection is contraindicated in patients with history of hypersensitivity reactions to VUEWAY.

Warnings and Precautions

There are **risks associated with intrathecal use** of GBCAs that can cause serious adverse reactions including death, coma, encephalopathy, and seizures. The safety and effectiveness of VUEWAY have not been established with intrathecal use and VUEWAY is not approved for intrathecal use.

Risk of **nephrogenic systemic fibrosis** is increased in patients using GBCA agents that have impaired elimination of the drugs, with the highest risk in patients with chronic, severe kidney disease as well as patients with acute kidney injury. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities.

Hypersensitivity reactions, including serious hypersensitivity reactions, could occur during use or shortly following VUEWAY administration. Assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders, administer VUEWAY only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, and observe patients for signs and symptoms of hypersensitivity reactions after administration.

Gadolinium retention can be for months or years in several organs after administration. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (brain, skin, kidney, liver and spleen). Minimize repetitive GBCA imaging studies, particularly closely spaced studies, when possible.

Important Safety Information continued on the next page

Important Safety Information continued

Acute kidney injury requiring dialysis has occurred with the use of GBCAs in patients with chronically reduced renal function. The risk of acute kidney injury may increase with increasing dose of the contrast agent.

Extravasation and injection site reactions can occur with administration of VUEWAY. Ensure catheter and venous patency before the injection of VUEWAY.

VUEWAY may **impair the visualization of lesions** seen on non-contrast MRI. Therefore, caution should be exercised when VUEWAY MRI scans are interpreted without a companion non-contrast MRI scan.

The most common adverse reactions (incidence \geq 0.5%) are injection site pain (0.7%), and headache (0.7%).

POST-MARKETING EVENTS

Acute pancreatitis within 48 hours of GBCA administration has been reported.

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 click [here](#) for full Prescribing Information for VUEWAY (gadopiclenol) solution for injection including BOXED WARNING on Nephrogenic Systemic Fibrosis.

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US-VW-2500002 3/25