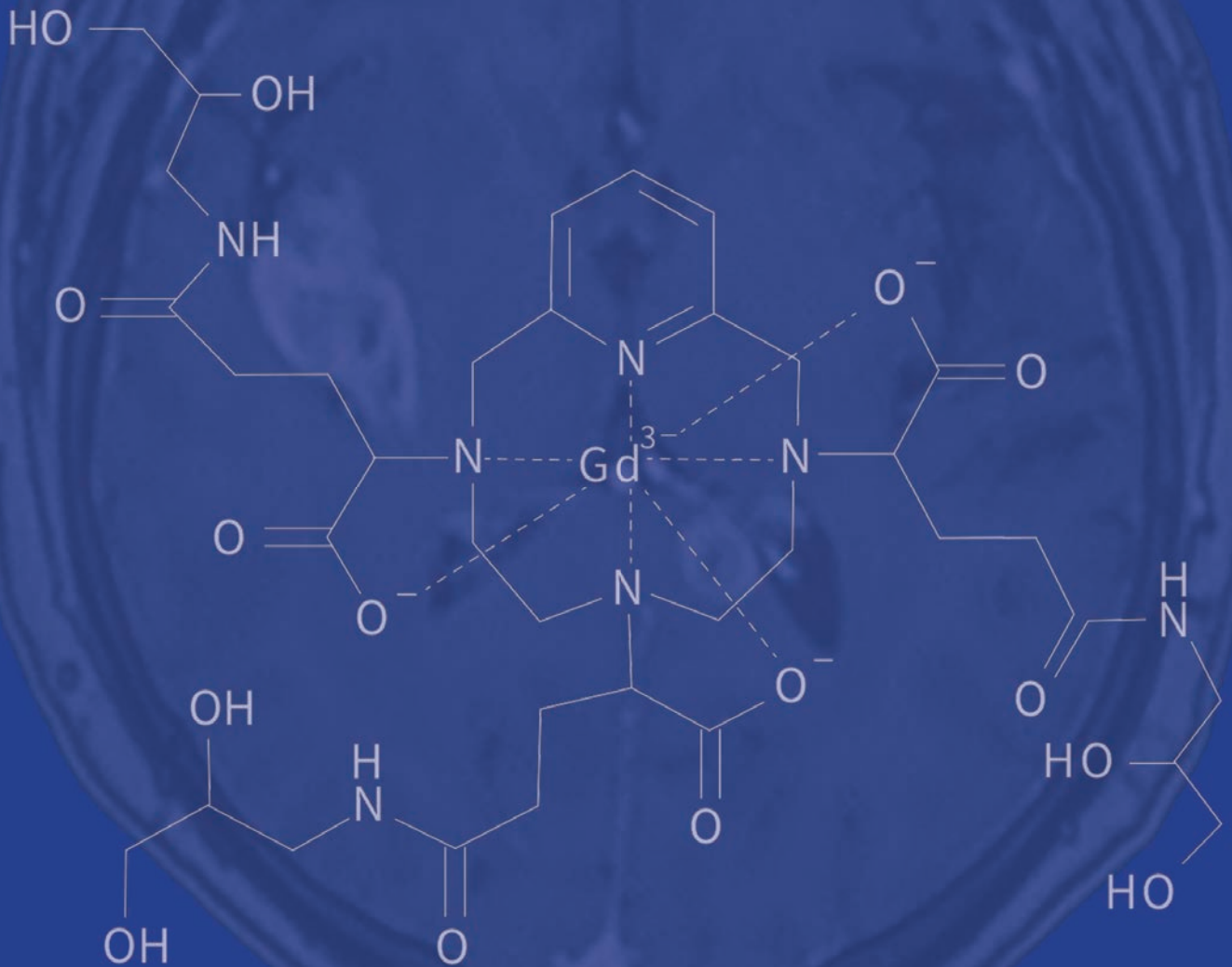


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The Journal of Practical Medical Imaging and Management

## Vueway™ (Gadopiclenol) Practical Considerations for Use



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## Vueway™ (Gadopiclenol): Practical Considerations for Use

### Program Description

Prior to 2023, six general-use, extracellular fluid magnetic resonance imaging (MRI) contrast agents were available in the United States: ProHance<sup>®</sup> (gadoteridol), Gadavist<sup>®</sup> (gadobutrol), Dotarem<sup>®</sup> (gadoterate meglumine; Clariscan™ (gadoterate meglumine); Omniscan™ (gadodiamide); and MultiHance<sup>®</sup> (gadobenate dimeglumine). These gadolinium-based contrast agents (GBCAs) vary with respect to chelate structure (ionic vs nonionic; macrocyclic vs linear), molar concentration (the number of Gd molecules per mL), and relaxivity. Of these, only the linear agent MultiHance was considered high relaxivity, with many intraindividual crossover comparison studies demonstrating greater signal-to-background with this agent. In addition, decades of use demonstrated that all of these GBCAs were quite safe; however, since 2006, concerns about the safety of GBCAs have come to light, particularly with regard to the less stable (linear, nonionic) agents. Specifically, nephrogenic systemic fibrosis (NSF) and Gd retention were seen to occur more readily with the use of these less-stable agents. As a result, it became apparent that a macrocyclic, high-relaxivity GBCA would be ideal, optimizing patient safety without compromising image quality. In 2023, the US Food and Drug Administration approved a new GBCA that represents a significant advance in terms of both efficacy and safety: the high-relaxivity, macrocyclic GBCA Vueway™ (gadopiclenol). This paper compares the properties, mechanism-of-action, dosing, efficacy, and safety of the currently available GBCAs to the new agent Vueway.

### Learning Objectives

At the conclusion of this activity, participants should be able to:

- Assess the properties, mechanism of action, and dosing of the available GBCAs;
- Explain the differences in safety among the GBCAs;
- Analyze the bases for the increased relaxivity of Vueway; and
- Summarize the intraindividual clinical trial results of Vueway vs the comparators MultiHance and Gadavist.

### Author

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# Vueway™ (Gadopiclenol): Practical Considerations for Use

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## Introduction

During the past several decades, advances in hardware and software have resulted in significant improvements in magnetic resonance image (MRI) quality. The performance of gadolinium (Gd)-based contrast agents (GBCAs), meanwhile, has remained largely the same. That changed first in 2004, with the approval of the high-relaxivity, linear agent MultiHance® (gadobenate dimeglumine), and then in 2023, when the high-relaxivity, macrocyclic agent Vueway™ (gadopiclenol) received US Food and Drug Administration (FDA) marketing approval. This paper reviews and compares the properties, mechanism-of-action, dosing, efficacy, and safety of Vueway with those of the six other GBCAs currently available in the US.

## GBCA Properties, Mechanism-of-Action, Dosing, and Efficacy






Prior to the introduction of Vueway, six general-use, extracellular fluid GBCAs were available in the United States: ProHance® (gadoteridol), Gadavist® (gadobutrol), Dotarem® (gadoterate meglumine); Clariscan™ (gadoterate meglumine); Omniscan™ (gadodiamide); and MultiHance® (gadobenate dimeglumine).<sup>1-6</sup> (Table 1) All of these agents utilize the Gd ion (<sup>64</sup>Gd) as the basis of enhancement.<sup>1-7</sup> Gadolinium is a rare earth metal with strong paramagnetic properties due to the seven unpaired

**Table 1.** Properties of Available Gadolinium-based Contrast Agents.<sup>1-10</sup>

Trade Name	Chemical Name	Structure	Ionicity	Molar Formulation	Standard Dose (mmol/kg)	r1 at 1.5T (mM <sup>-1</sup> s <sup>-1</sup> )**	Kinetic Stability (T <sub>1/2</sub> ) <sup>†</sup>	ACR Group
ProHance	Gadoteridol	Macrocyclic	Nonionic	0.5	0.1	4.1	4 hr	I
Gadavist	Gadobutrol	Macrocyclic	Nonionic	1.0	0.1	5.2	18 hr	I
Dotarem/ Clariscan*	Gadoterate meglumine	Macrocyclic	Ionic	0.5	0.1	3.6	4 days	I
Omniscan	Gadodiamide	Linear	Nonionic	0.5	0.1	4.3	<5 sec	II
MultiHance	Gadobenate dimeglumine	Linear	Ionic	0.5	0.1	6.3	<5 sec	I
Vueway	Gadopiclenol	Macrocyclic	Nonionic	0.5	0.05	12.8	20 days	I

\*Clariscan is the generic formulation of Dotarem; \*\*Measured at 37°C; †Measured at pH1.0, 25°C.

**Figure 1.** Relaxivities, concentrations, and approved doses of Vueway vs other GBCAs.<sup>1-10</sup>

Contrast Agent	Vueway (gadopiclenol)	Gadavist (gadobutrol)	ProHance (gadoteridol)	MultiHance (gadobenate dimeglumine)	Dotarem/ Clariscan (gadoterate meglumine)
Relaxivity	11.6–13.2*	5.0–6.1*	3.7–4.8*	5.5–9.2*	3.5–4.3*
Concentration	0.5M	1.0M	0.5M	0.5M	0.5M
Dose	0.05 mmol/kg	0.1 mmol/kg	0.1 mmol/kg	0.1 mmol/kg	0.1 mmol/kg
					

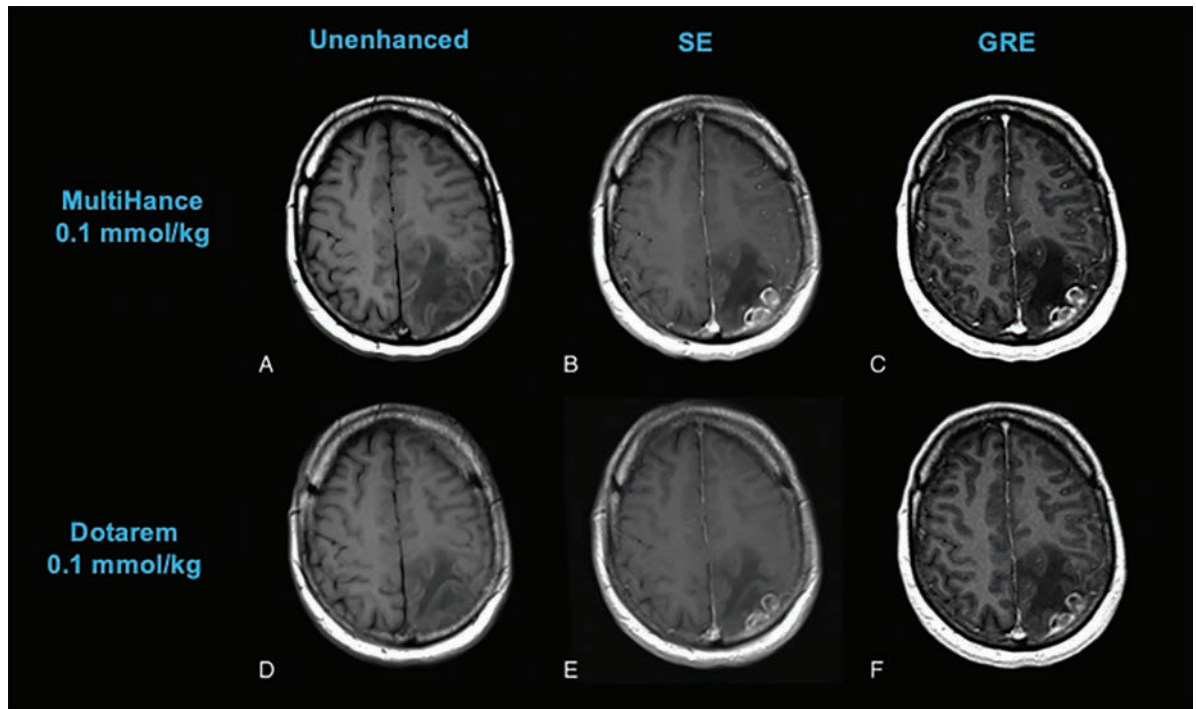
\*Depending on field strength.

electrons in the orbital shell.<sup>11</sup> The most common oxidized form has a +3 charge, which has a similar ionic radius as the divalent form of calcium, a critical mineral in the human body. Thus, Gd is a potent calcium antagonist *in vivo*; in order to be used safely as an MRI contrast agent, the Gd ion must be made physiologically inert.<sup>11-13</sup> This is achieved by binding the Gd ion to a large organic molecule known as a ligand. The Gd ion plus the ligand

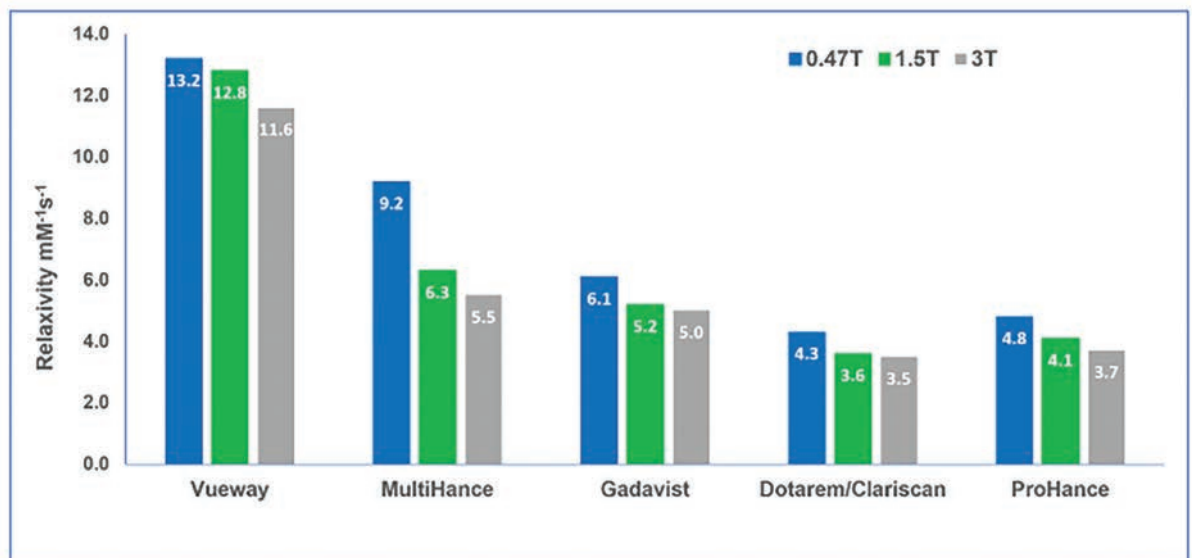
are together referred to as a chelate. The chelate allows for safe elimination of the potentially toxic Gd ion from the body, primarily via the kidneys.<sup>11</sup>

As shown in Table 1, GBCAs vary in their chelate structure (ionic vs nonionic; macrocyclic vs linear) and molar concentration (the number of Gd molecules per mL).<sup>8,9</sup> All are formulated at a concentration of 0.5M, with the exception of Gadavist, which is formulated at a

**Figure 2.** Unenhanced, SE (spin echo), and GRE (gradient echo) images obtained with equivalent 0.1 mmol/kg doses of MultiHance and Dotarem, demonstrating the benefit of high relaxivity.<sup>24</sup>



**Figure 3.** Relaxivities of GBCAs at various field strengths (at 37° C in biological medium).<sup>9</sup>



concentration of 1M. (Figure 1) This difference in molar concentration is important in that, with respect to Gadavist vs the 0.5M agents, the same volume of each agent does not deliver the same dose of Gd. Indeed, the dose is determined not by the volume (mL) of the agent itself but by

the amount of Gd it delivers (in units of mmol/kg). Thus, administering an approved 0.1 mmol/kg dose of 1M Gadavist results in a lower volume of the agent being delivered, not a lower dose of Gd. This is depicted graphically in Figure 1: an approved dose of Gadavist delivers the same dose of

Gd, just at half the volume. Note that Vueway is 0.5M, but due to its much higher relaxivity, an approved dose is half that of the other agents. This is discussed in more detail below.

Gadolinium-based contrast agents work by shortening the T1- and T2-relaxation times of water-based

**Table 2.** Contrast-to-Noise Ratio Results from Adult Phase II Dose-Finding Study of Vueway vs 0.1 mmol/kg MultiHance.<sup>50</sup>

Reader	Vueway Dose (mmol/kg)	n	Vueway	MultiHance	P
1	0.2	44	49.99	35.55	<0.0001
	0.1	51	35.94	27.28	0.0007
	0.05	56	31.78	29.60	0.1858
	0.025	54	21.13	31.72	----
2	0.2	41	103.18	64.81	0.0002
	0.1	43	72.17	52.79	<0.0001
	0.05	47	51.02	49.11	0.3384
	0.025	44	43.15	57.29	----
3	0.2	42	125.08	73.12	<0.0001
	0.1	45	94.17	64.94	<0.0001
	0.05	51	67.05	64.58	0.3249
	0.025	49	46.74	70.70	----

hydrogen protons.<sup>14</sup> For the remainder of this article, only the T1-shortening effects will be addressed. When the large GBCA molecule comes within approximately 3 angstroms of a water molecule, the water molecule is incorporated into the inner sphere of the GBCA.<sup>15,16</sup> The molecular tumbling rate of the water molecule slows, resulting in a significant shortening of the T1-relaxation time of the water-based hydrogen proton. The relaxivity ( $r_1$ ) of a GBCA is a measurable characteristic of all GBCAs, reflecting the amount of T1-shortening of water-based protons for a given dose. The altered T1-relaxation time is inversely related to the relaxivity ( $r_1$ ) of the GBCA. The higher the relaxivity ( $r_1$ ), the shorter the T1-relaxation time of the water-based hydrogen protons. Higher relaxivity results in a greater signal-to-background ratio (ie, higher contrast) when acquiring images with appropriate T1 weighting.<sup>15,16</sup>

Given that conventional GBCAs interact with a single water molecule, increasing the number of Gd molecules will involve more

water molecules, thereby increasing the effect.<sup>15-18</sup> This has been clearly demonstrated in ProHance dosing studies (up to 0.3 mmol/kg).<sup>19</sup> Note that as of this writing, ProHance is the only agent for which such triple dosing (0.3 mmol/kg) is included in the label.<sup>1</sup>

Until last year, the conventional-relaxivity GBCAs were those with relaxivities ( $r_1$  at 1.5T) ranging from a low of 3.9 mM<sup>-1</sup>s<sup>-1</sup>, for Dotarem/Clariscan, up to 4.6 mM<sup>-1</sup>s<sup>-1</sup> for Gadavist and 6.2 mM<sup>-1</sup>s<sup>-1</sup> for the high-relaxivity agent MultiHance.<sup>1-10</sup> (Table 1) The higher relaxivity of MultiHance results from its unique molecular structure, which includes an additional side chain that allows for weak and transient protein interaction, further increasing the effective size of the molecule. This results in a slower tumbling rate, greater T1 shortening, and almost twice the relaxivity of other conventional-relaxivity agents.<sup>20</sup> (Table 1) As expected, when administered at the approved dose of 0.1 mmol/kg, MultiHance has been demonstrated in many intraindividual crossover studies (in which the same patient

receives two MRI exams within several days, one with each GBCA) to result in increased lesion sensitivity and conspicuity.<sup>21-26</sup> (Figure 2)

MultiHance can also be used to reduce the Gd dose, as a lower dose of MultiHance has demonstrated efficacy equivalent to the higher dose of a conventional-relaxivity GBCA.<sup>27-30</sup> Note that Gadavist is marketed as a high-relaxivity agent, but it has no protein interaction, and its relaxivity is only slightly higher than the other nonprotein-interacting agents. (Table 1) Moreover, in intraindividual crossover studies, the efficacy of Gadavist has been shown to be comparable to conventional-relaxivity agents but lower than the high-relaxivity GBCA MultiHance.<sup>26,32</sup>

### GBCA Stability and Safety

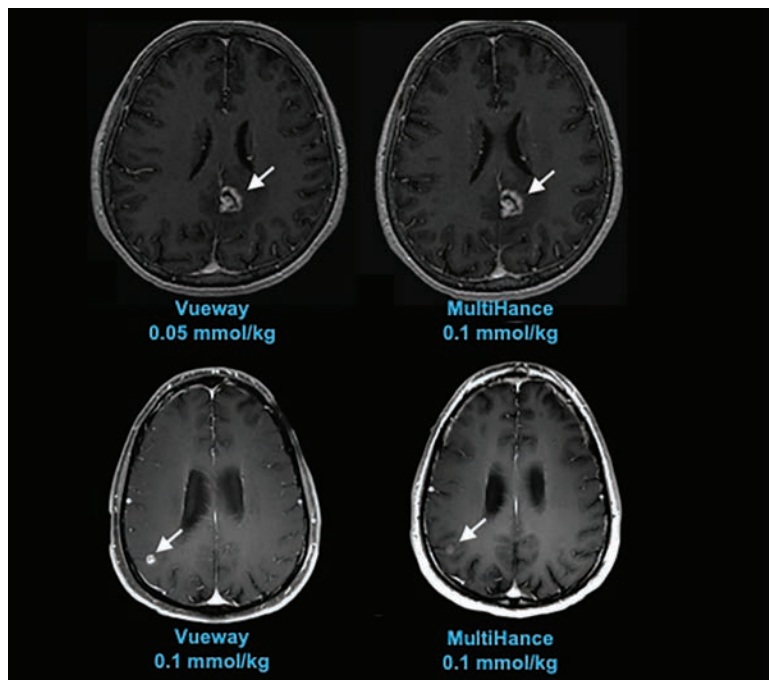
Owing to differences in the molecular structure of GBCAs, the propensity of the ligand to release the Gd ion—ie, the agent's stability—varies. There are two major stability metrics, both measured in the laboratory (ie, in vitro): the thermodynamic stability constant

and the kinetic stability constant.<sup>33</sup> Thermodynamic stability reflects the energy required to release the Gd ion and, when measured at a biological pH (pH=7.4), is referred to as the conditional thermodynamic stability constant. Kinetic stability reflects the rate or speed at which a given agent begins to disassociate the Gd ion from the ligand. Because the disassociation half-life for many agents is very long—hundreds of years—the kinetic stability of these agents is typically measured under chemically stressful conditions (pH=1). Of these two metrics, kinetic stability is considered to be the most significant *in vivo*.<sup>33</sup> Based on these *in vitro* stability constants, the ionic, macrocyclic GBCAs have the highest stability, and the nonionic, linear GBCAs have the lowest stability, with the remainder having intermediate stability. (Table 1) Note that the key metric, the kinetic stability constant, is highest with the macrocyclic agents, regardless of ionicity.

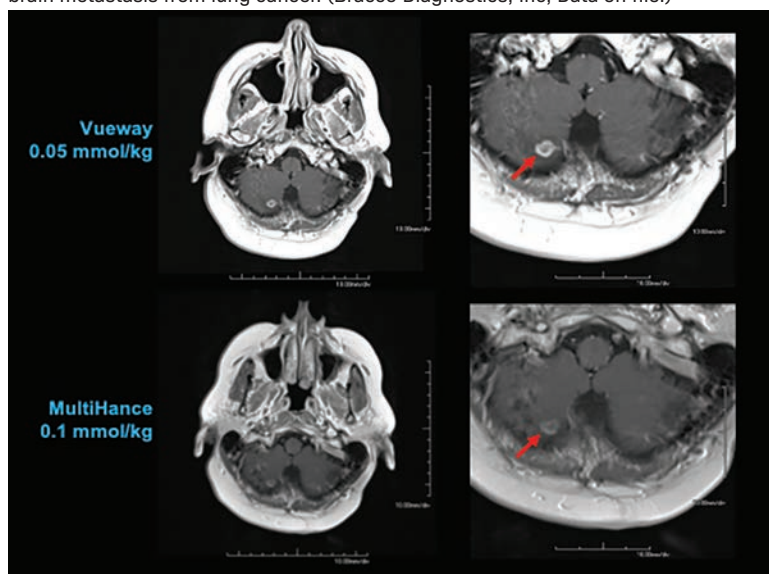
*In vivo* assessments of stability focus on an organometallic reaction known as transmetallation. This is where a competitor, typically a metal found normally in the body (eg, iron, magnesium, copper, zinc, or calcium) displaces the Gd in the chelate and binds to the ligand, resulting in the release of free Gd.<sup>17,34</sup> As expected, transmetallation has been shown to occur more readily with the less-stable GBCAs.<sup>17,34</sup>

GBCAs have long been considered extremely safe; however, concerns about their use began coming to light in 2006, particularly in vulnerable patient populations. Specifically, two related phenomena have been observed in patients administered lower-stability GBCAs. First, nephrogenic systemic fibrosis (NSF), a progressive and potentially fatal connective tissue disease, has been observed almost exclusively in patients with poor renal function who are administered repeat

**Figure 4.** 3D GRE contrast-enhanced MRI scans of patients with brain lesions. Top two images, 65-year-old female patient with brain metastasis from lung cancer; bottom two images, 38-year-old male patient with brain metastasis from lung cancer.<sup>51</sup>



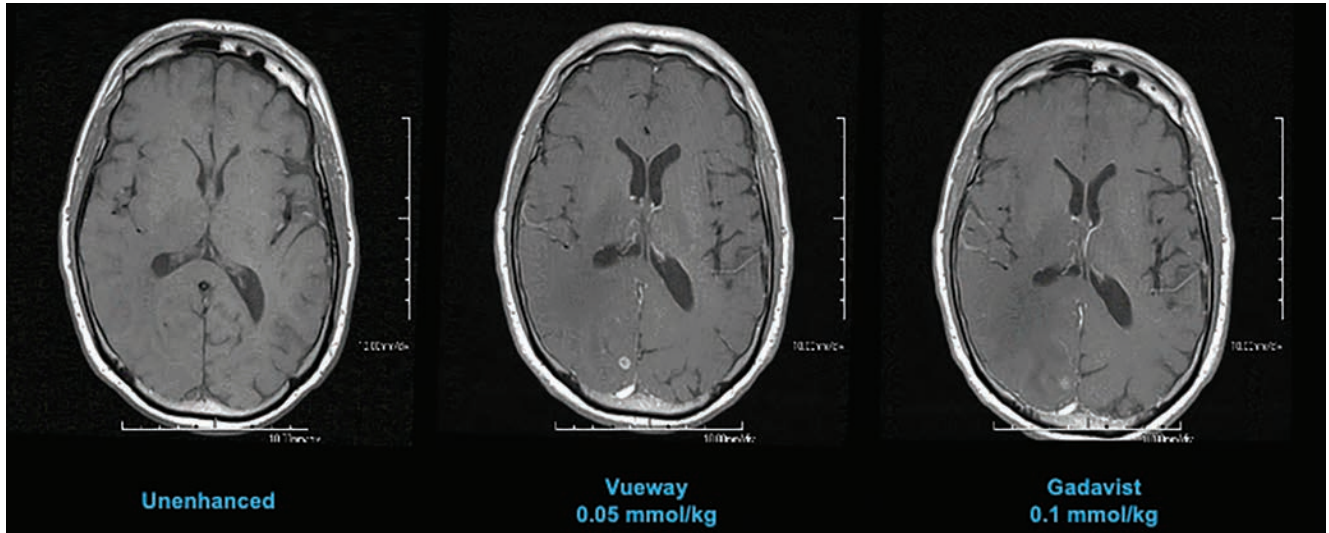
**Figure 5.** Contrast-enhanced T1 SE MRI scans of 63-year-old female with brain metastasis from lung cancer. (Bracco Diagnostics, Inc; Data on file.)



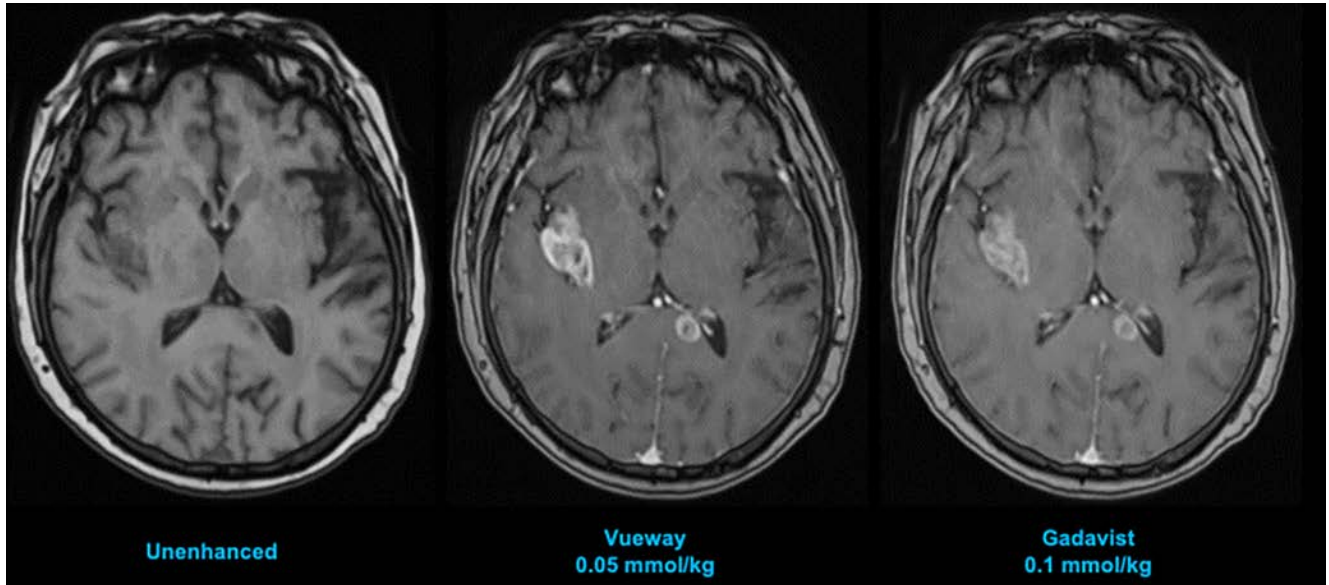
and/or higher doses of the least-stable GBCAs Omniscan, OptiMARK, and Magnevist (OptiMARK and Magnevist are no longer available in the US).<sup>10,35,36</sup> Based on NSF risk, the American College of Radiology (ACR) has classified the available GBCAs

into two groups; those with the highest risk for causing NSF (Group I: Omniscan, Magnevist, OptiMARK) and those with the lowest risk (Group II: MultiHance, Gadavist, Dotarem/Clariscan, ProHance, Vueway/Elucirem). In addition, the FDA has

**Figure 6.** T1 SE contrast-enhanced 3T MRI scans of 65-year-old male with brain metastases from lung adenocarcinoma. (Bracco Diagnostics, Inc; Data on file.)



**Figure 7.** T1 SE contrast-enhanced MRI scans of 62-year-old female with right frontal high-grade glial tumor. (Bracco Diagnostics, Inc; Data on file.)



contraindicated the highest-risk GBCAs in at-risk patients; ie, those with acute or chronic severe kidney dysfunction.<sup>10,37</sup>

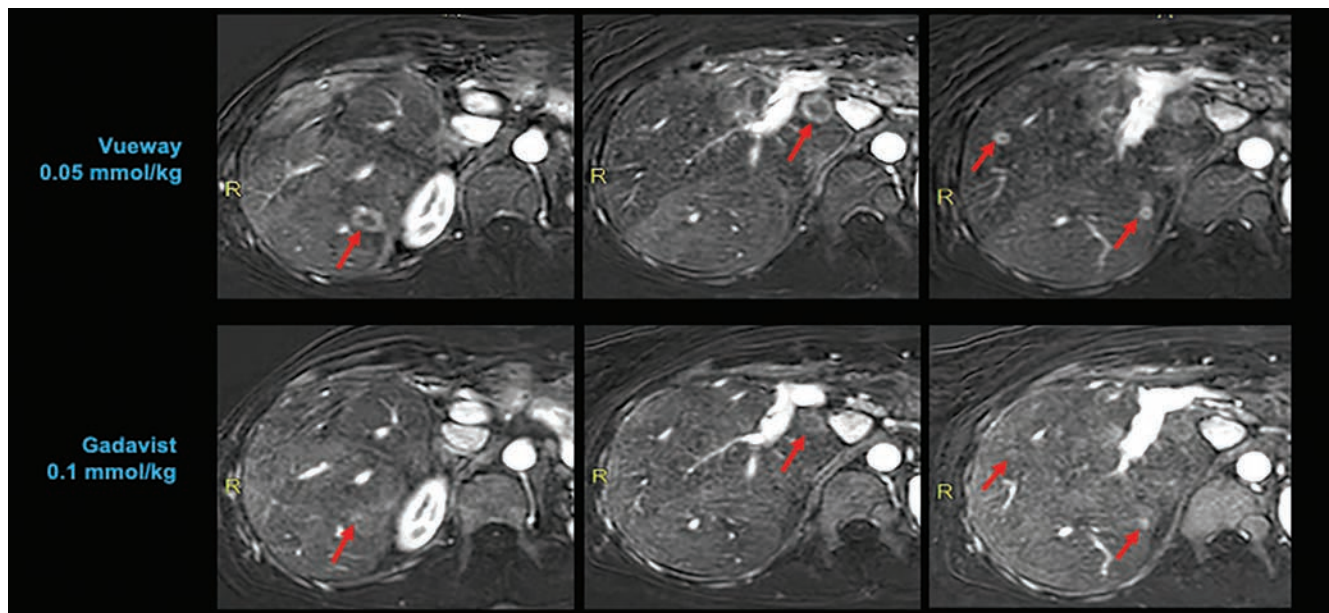
Although the pathophysiology of NSF is not well understood, it is believed that GBCAs are not readily eliminated by patients with poor renal function. This, combined with the lower stability of the GBCA, is believed to initiate a fibrotic cascade in tissues.<sup>38</sup> Nephrogenic systemic fibrosis has largely been eliminated,

thanks to changes in patient management, including screening at-risk patients and limiting use of the less-stable GBCAs.<sup>39</sup> Many practices have shifted away from linear agents in favor of macrocyclic agents, particularly in patients with poor renal function, in those requiring repeat scans, and in children,<sup>40</sup> despite the fact that the linear agent MultiHance belongs to Group II.

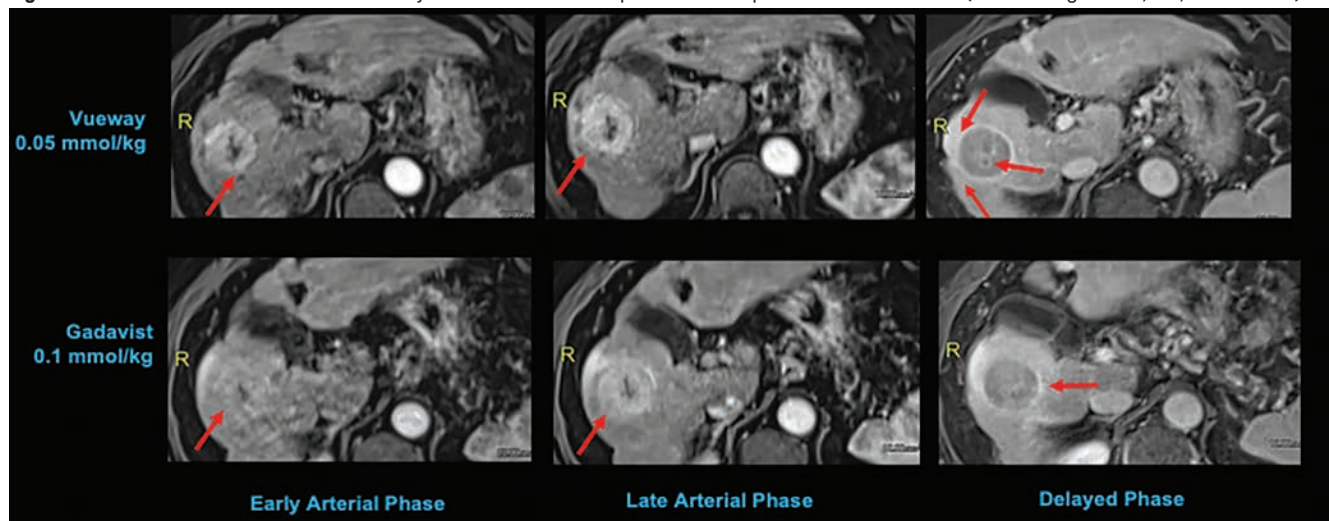
Further fueling the movement toward macrocyclic agents was the

discovery that small amounts of Gd are retained in certain areas of the brain and body. While it has been known for decades that Gd can be found in bone and other organs following GBCA administration,<sup>34,41,42</sup> retention in the brain of patients without blood-brain barrier disruption was completely unexpected.<sup>43</sup> Sensitive assays have detected Gd in the brain after administration of all GBCAs;<sup>44</sup> however, similar to that seen with NSF, the less-stable agents

**Figure 8.** Contrast-enhanced, arterial-phase MRI scans of 61-year-old male with cholangiocarcinoma. (Bracco Diagnostics, Inc; Data on file.)



**Figure 9.** Contrast-enhanced MRI scans of 66-year-old male cirrhotic patient with hepatocellular carcinoma. (Bracco Diagnostics, Inc; Data on file.)



were associated with higher levels of Gd retention.<sup>43,45-47</sup> Notably, there is no evidence to date of clinically significant sequelae related to Gd retention. Nevertheless, the ACR and the FDA have issued warnings that GBCAs should be administered only when deemed necessary and only at the lowest dose necessary for diagnosis.<sup>10,48</sup>

Given all that is known regarding the characteristics and safety of GBCAs, the need for a macrocyclic, high-relaxivity GBCA that can limit

patient exposure to Gd without compromising image quality has become increasingly apparent.

### Vueway

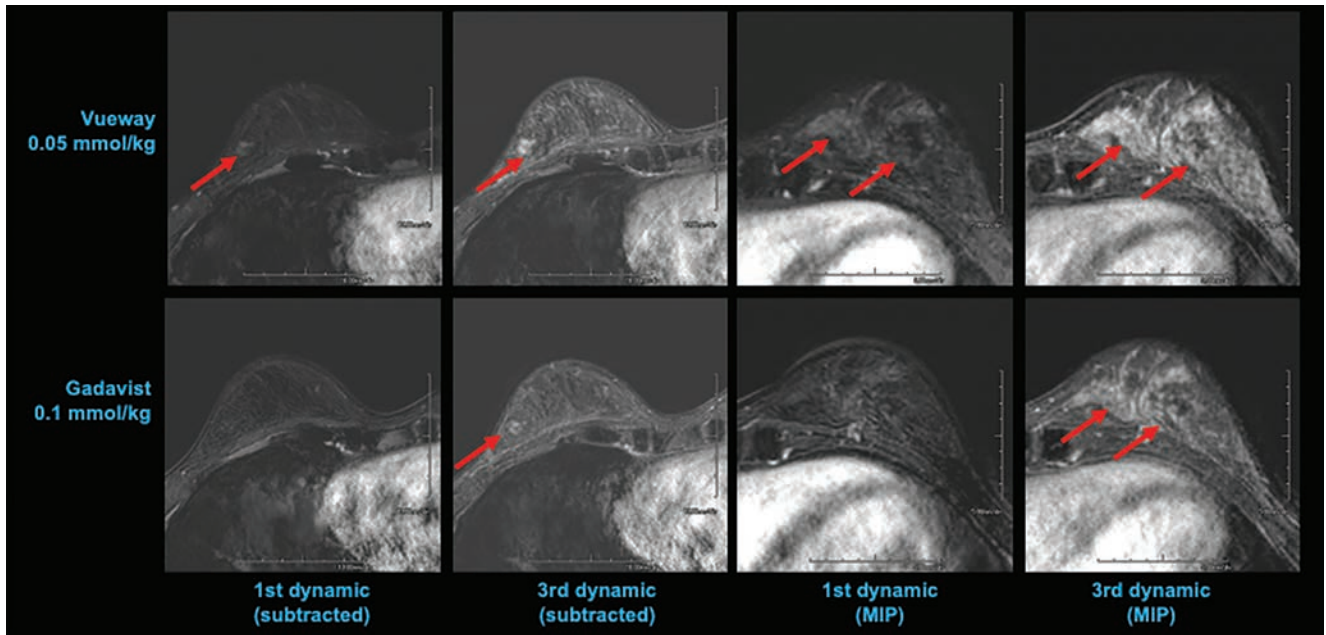
Vueway is a macrocyclic GBCA (like ProHance, Gadavist, and Dotarem/Clariscan) with high kinetic stability (higher than ProHance, Gadavist, and Dotarem/Clariscan).<sup>8</sup> (Table 1) Owing to the agent's high stability, the latest version of the *ACR Contrast Media Manual* has classified

Vueway as a Group II agent, the safest class of GBCAs.<sup>10</sup> In addition, it has very high relaxivity (over twice that of the high-relaxivity GBCA MultiHance), and this high relaxivity persists at higher field strengths.<sup>8</sup> (Table 1; Figure 3) With respect to Gd retention in the brain, a study in rats demonstrated that, like other macrocyclic GBCAs, only a very small amount of retention was attributable to Vueway.<sup>49</sup>

There are several bases for the higher relaxivity seen with Vueway.



**Figure 10.** Contrast-enhanced MRI scans of 34-year-old female with fibroadenoma in right breast and multicentric cancer (3T). (Bracco Diagnostics, Inc; Data on file.)



First, it has a  $q$  value of 2, which means it incorporates two water molecules within its inner hydration sphere, as opposed to the other agents, which allow only one water molecule within their inner hydration sphere.<sup>8,18</sup> Second, the Vueway molecule has three hydrophilic arms, allowing for interaction with more water molecules in its outer sphere.<sup>8</sup> Finally, the larger molecule size of Vueway results in an even slower molecular tumbling rate.<sup>8,18</sup>

Note that the recommended dosing for Vueway included in the labeling could have been equivalent to the approved dose of the other GBCAs (0.1 mmol/kg), with the expectation that contrast enhancement would be superior. However, due to concerns about Gd exposure in patients, the recommended dosing is actually half (0.05 mmol/kg) the recommended dose of the other extracellular agents; therefore, the recommended volume delivered to achieve approved dosing is comparable to the 1M agent Gadavist.<sup>7</sup> (Table 3)

One would expect from the higher relaxivity of Vueway that it

**Table 3.** Dosing of Vueway vs Other GBCAs.<sup>1-4,6,7</sup>

Agent	Gd Concentration (mg/mL)	Volume for 80 kg patient (mL)	Total Gd (mg)
<b>ProHance Dotarem/Clariscan</b>	<b>78.625</b>	<b>16</b>	<b>1107.50</b>
<b>MultiHance</b>	<b>78.625</b>	<b>16</b>	<b>1107.50</b>
<b>Gadavist</b>	<b>157.25</b>	<b>8</b>	<b>1107.50</b>
<b>Vueway</b>	<b>78.625</b>	<b>8</b>	<b>550.375</b>

would perform better than MultiHance or conventional GBCAs at a comparable dose and perform comparably at a lower dose. In an adult phase 2 dosing study, 272 subjects with known or suspected brain lesions were randomized to receive one of four body-weight doses of Vueway—0.2 mmol/kg; 0.1 mmol/kg; 0.05 mmol/kg; or 0.025 mmol/kg—vs a single 0.1 mmol/kg dose of MultiHance.<sup>50</sup>

The results from three blinded readers are shown in Table 2. When comparing 0.1 mmol/kg MultiHance to the lowest dose of Vueway (0.025 mmol/kg), all three

readers rated the contrast enhancement greater with MultiHance; however, images acquired using 0.05, 0.1, or 0.2 mmol/kg Vueway all showed greater enhancement than those acquired using MultiHance, with 0.1 and 0.2 mmol/kg doses demonstrating significantly better enhancement.<sup>50</sup> Examples of paired images (0.1 mmol/kg MultiHance vs 0.05 or 0.1 mmol/kg Vueway) are shown in Figures 4 and 5.<sup>50</sup>

Phase III intraindividual clinical trials comparing Gd retention in the brain and other parts of the body with Vueway vs Gadavist have also been performed. Specifically, the

safety and effectiveness of Vueway for lesion visualization was evaluated in two prospective, double-blind, randomized, crossover clinical studies.<sup>7,51,52</sup> Study 1 (NCT03996447; the PICTURE Trial) was performed in 256 adults with known or highly suspected CNS lesions with focal areas of disruption of the blood-brain barrier.<sup>51</sup> Study 2 (NCT03986138; the PROMISE Trial) was performed in 273 adults with suspected enhancing abnormalities in at least one body region among the head and neck, thorax, abdomen, pelvis, and musculoskeletal system.<sup>52</sup> In each study, patients received both 0.05 mmol/kg Vueway and 0.1 mmol/kg Gadavist in randomized order separated by 2 days to 14 days.<sup>7,51,52</sup> Magnetic resonance imaging was performed before and after administration of each contrast agent. Precontrast and paired (consisting of both precontrast and postcontrast images for the same drug) image sets were independently evaluated by three central readers who were blinded to the identity of the contrast agent.<sup>7,51,52</sup> Readers scored up to three lesions per patient for border delineation, internal morphology, and contrast enhancement, each on a scale from 1 to 4.<sup>7,51,52</sup> In all cases, the approved 0.05 mmol/kg dose of Vueway performed better at the quantitative level than the approved 0.1 mmol/kg dose of the conventional-relaxivity comparator Gadavist.<sup>7,51,52</sup> Analysis of visualization endpoints led to non-inferiority.<sup>7,51,52</sup> Examples of paired images from these brain and body studies are shown in Figures 6-10.<sup>51,52</sup> Moreover, in both the PICTURE and the PROMISE trials, the safety profile of Vueway was similar to that of Gadavist, with rare and mostly mild side effects.<sup>51,52</sup>

## Conclusion

With its macrocyclic structure, high relaxivity and stability, and lower approved dose, Vueway is the ideal contrast agent for MRI. The risk of NSF and Gd retention is low, and the lower approved dosing reduces patient exposure to Gd without sacrificing image quality or lesion conspicuity.

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