Gadolinium-based contrast agents

May 2023

Executive Summary

- There are 7 FDA-approved gadolinium-based contrast agents (GBCAs) that are supplied as 10 products. Gadoterate meglumine is supplied as 3 different products, including a branded product (Dotarem, Guerbet) and 2 bioequivalent, generic products (Clariscan, GE; gadoterate meglumine, Fresenius Kabi). Gadopiclenol was co-developed by Bracco and Guerbet and each company is commercializing the product independently under different brand names (Elucirem, Guerbet; Vueway, Bracco).
- The GBCAs share a common structure, a gadolinium ion chelated to an organic ligand, and a common mechanism of action. Except for gadoxetate (Eovist), a liver specific agent, the remainder of the GBCAs are extracellular agents that are approved for visualization of CNS lesions. A few of the extracellular agents are also approved for non-CNS MR imaging and include gadobutrol (Gadavist), gadopiclenol (Elucirem, Vueway), gadodiamide (Omniscan), and gadoteridol (ProHance). Gadopiclenol is the first GBCA to be broadly approved to visualize lesions located throughout the body, including a first in class approval for visualization of musculoskeletal lesions. Gadobutrol and gadobenate dimeglumine (MultiHance) are additionally approved for use with MR angiography.
- The GBCA agents are differentiated by chelate structure, gadolinium-chelate stability, viscosity, ionicity, osmolality, volume of distribution, and relaxivity. Properties such as chelate structure, thermodynamic and kinetic stability, viscosity, and ionicity mainly impact GBCAs' safety profile while differences in relaxivity may impact tissue enhancement.
- In conventional CNS imaging, r1 relaxivity (vs concentration) is the primary determinant of contrast-enhancing capability. Most GBCAs have similar r1 relaxivity apart from gadopiclenol and gadobenate dimeglumine, which have higher r1 relaxivities due to protein binding and water exchange kinetics, respectively. Relative to the relaxivities of other GBCAs, the relaxivity of gadopiclenol is approximately 2 to 3 times higher while that of gadobenate dimeglumine is approximately 1.5 times higher.
- In comparative studies of conventional MR imaging, blinded readers significantly preferred gadobenate dimeglumine vs standard relaxivity GBCAs for qualitative and quantitative endpoints. Half-dose gadopiclenol was non-inferior to standard-dose gadobutrol for qualitative visualization endpoints in phase 3 studies of the CNS and body. Because qualitative endpoints are surrogates, it is unclear if greater signal intensity enhancement leads to improvements in clinically important outcomes such as lesion detection, patient management, and/or surgical planning. Therefore, the extracellular GBCAs are considered mostly interchangeable for CNS imaging from a diagnostic standpoint (albeit safety differences exist).
- While preliminary data from a phase 2 dose finding study suggest that gadopiclenol is superior to gadobenate dimeglumine for quantitative and qualitative endpoints when given at equimolar doses, Guerbet pursued approval based on equivalence of gadopiclenol at half dose with the goal of reducing patient exposure to gadolinium. It is uncertain if the superior signal enhancement with standard-dose gadopiclenol is associated with superior diagnostic efficacy.
- In dynamic imaging applications, gadobenate dimeglumine has been associated with higher signal enhancement and/or signal loss compared with standard relaxivity GBCAs. While GBCAs with a higher concentration (gadobutrol) may theoretically confer a benefit in dynamic imaging applications by improving bolus geometry, results of interindividual comparisons have been discordant.
- Based on safety results of intraindividual comparisons, the incidence of acute adverse events does not differ among GBCAs.

- Gadolinium exposure has been associated with the development of nephrogenic systemic fibrosis (NSF). Because the largest number of unconfounded cases of NSF have occurred after exposure to certain linear agents that include gadodiamide, gadopentetate (Magnevist, withdrawn), and gadoversetamide (OptiMark, withdrawn) and the fewest cases have occurred with macrocyclic agents, the prevailing theory is that the development of NSF in patients with risk factors (eg, on dialysis, severe or end-stage chronic kidney disease, acute kidney injury) is inversely related to the stability of the gadolinium-chelate complex.
- The American College of Radiology (ACR) strongly prefers the use of group II agents (gadoterate meglumine, gadobutrol, gadobenate dimeglumine, gadoteridol, gadopiclenol) in patients at risk for NSF. However, if a group I or III agent must be used in patients at risk, the potential benefit of a GBCA-enhanced exam should be weighed against the individual risk of NSF and informed consent should be obtained.
- After administration, all GBCAs, regardless of structure or ionicity, are associated with some degree of residual gadolinium in the brain and other tissues. Chelation of residual gadolinium with macromolecules appears to be higher after administration of linear GBCAs than after macrocyclic GBCAs. Based on animal studies, gadopiclenol appears to have similar washout kinetics as gadobutrol when administered at equimolar doses.
- Due to the unknown clinical significance of residual gadolinium deposits, many facilities have adopted policies that encourage the use of macrocyclic agents. The ACR and International Society of Magnetic Resonance in Medicine suggest that when selecting a GBCA, many factors should be considered, including pharmacokinetics, relaxivity, efficacy, potential adverse events, patient age, probability of need for repeated examinations, cost, and the propensity of an agent to deposit gadolinium.
- Gadopiclenol is a new macrocyclic option with high relaxivity and high kinetic inertness. It demonstrates similar contrast enhancement at half the gadolinium dose as other GBCAs. While it is unknown if the lower exposure to gadolinium reduces the incidence of clinically significant safety events, reduced gadolinium exposure may be an important consideration in patients at risk for development of NSF or in patients who will require repeated examinations using contrast. Beyond these patient groups, it is uncertain if gadopiclenol confers a benefit over other group II agents. While it does have an expanded indication for whole body imaging, extracellular GBCAs are often used off-label. Therefore, it is uncertain if gadopiclenol’s expanded approval is a differentiator.
- Gadobutrol is expected to lose exclusivity during the first half of 2023 and the FDA has granted effective approval to 2 abbreviated new drug applications. The potential for generic entrants and associated cost savings should be weighed in formulary decisions.

Gadolinium-based contrast agent side-by-side comparison

Brand name (generic name)	Dotarem, Clariscan (gadoterate meglumine)	Elucirem, Vueway (gadopiclenol)	Eovist (gadoxetate disodium)	Gadavist (gadobutrol)	MultiHance (gadobenate dimeglumine)	Omniscan (gadodiamide)	ProHance (gadoteridol)
Manufacturer	Guerbet LLC (Dotarem), GE Healthcare (Clariscan), Fresenius Kabi (gadoterate)	Guerbet LLC (Elucirem), Bracco (Vueway)	Bayer Healthcare Pharmaceuticals Inc	Bayer Healthcare Pharmaceuticals Inc	Bracco	GE Healthcare	Bracco
US market share (2022)[a]	• Clariscan (9.29%) • Dotarem (18.77%) • Gadoterate (<1%)	No data available	--	45.68%	14.07%	0.55%	11.65%
FDA-approved indications	Adults and pediatrics (including term neonates) • MRI: To detect and visualize areas with disruption of the BBB and/or abnormal vascularity in the brain, spine, and associated tissues	Adults and pediatrics ≥ 2 y • MRI: To detect and visualize lesions with abnormal vascularity in the central nervous system (brain, spine, and associated tissues) • MRI: body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system)	Adults MRI: To detect and characterize lesions in patients with known or suspected focal liver disease	Adults and pediatrics (including term neonates) • MRI: To detect and visualize areas with disrupted BBB and/or abnormal vascularity of the CNS • MRA: To evaluate known or suspected supra-aortic or renal artery disease Adults • MRI: To assess the presence and extent of malignant breast disease • MRI: To assess myocardial perfusion (stress, rest) and late gadolinium enhancement in adult patients with known or suspected CAD	Adults and pediatrics (including term neonates) • MRI: To visualize lesions with abnormal BBB or abnormal vascularity of the brain, spine, and associated tissues Adults • MRA: To evaluate known or suspected renal or aorto-ilio-femoral occlusive vascular disease	Adults and pediatrics ≥ 2 y • MRI: To visualize lesions with abnormal vascularity in the brain, spine, and associated tissues • MRI: To facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space	Adults and pediatrics (including term neonates): • MRI: To visualize lesions with disrupted of the BBB and/or abnormal vascularity in the brain (intracranial lesions), spine and associated tissues Adults • MRI: To visualize lesions in the head and neck

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Dosage and administration							
Dose	Adult and pediatric patients: 0.2 mL/kg (0.1 mmol/kg)	Adult and pediatric patients: 0.1 mL/kg (0.05 mmol/kg)	Adult patients: 0.1 mL/kg	Adult and pediatric patients: 0.1 mL/kg (0.1 mmol/kg, unless otherwise noted)	• Adult and pediatric patients ≥ 2 y: 0.2 mL/kg (0.1 mmol/kg) • Pediatric patients < 2 y: 0.1-0.2 mL/kg	• CNS, adult and pediatric patients: 0.2 mL/kg (0.1 mmol/kg) • Body, adult and pediatric patients: 0.2 mL/kg (0.1 mmol/kg) • Kidney, adult and pediatric patients: 0.1 mL/kg (0.05 mmol/kg)	• Adult and pediatric patients: 0.2 mL/kg (0.1 mmol/kg) • A supplementary dose of 0.4 mL/kg may be given up to 30 min after the first dose in adult patients with normal renal function and negative or equivocal MRI of the CNS
Administration – CNS imaging	• Administer as an IV bolus injection, manually or power injection, at a flow rate of 2 mL/sec for adult and 1-2 mL/sec for pediatric patients • Follow with a normal saline flush	• Administer as an IV bolus injection, manually or by power injector, at a flow rate of 2 mL/sec. • Follow with a normal saline flush	--	• Administer as an IV injection, manually or by power injector, at a flow rate of approximately 2 mL/sec • Follow with a normal saline flush	• Administer as an IV bolus injection • Follow the injection with a saline flush of at least 5 mL	• Administer as an IV bolus injection • Follow the injection with a saline flush of at least 5 mL	• Administer as a rapid IV infusion (10 mL/min-60 mL/min) or bolus (> 60 mL/min) • Follow the injection with a saline flush of at least 5 mL
Administration – non-CNS imaging	--	Same as for CNS imaging	MRI of the liver • IV bolus at a flow rate of 2 mL/sec, followed by a normal saline flush	MRI of the breast • IV bolus by power injector, followed by a normal saline flush MRA • Adults: Administer by power injector, at a flow rate of 1.5 mL/sec, followed by a 30 mL normal saline flush • Pediatrics: Administer by power injector or	MRA • IV bolus, manually or power injector, followed by at least 20 mL saline flush	MRI of body (intrathoracic), intra-abdominal, and pelvic cavities • IV bolus followed by at least 5 mL saline flush MRI of the kidney • IV bolus followed by at least 5 mL saline flush	MRI of extracranial/extraspinal tissues • Rapid IV infusion (10 mL/min-60 mL/min) or bolus (> 60 mL/min), followed by 5 mL saline flush

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				manually, followed by a normal saline flush Cardiac MRI • Administer through a separate IV line in the contralateral arm if providing a continuous infusion of a stress agent • Administer as 2 separate bolus injections of 0.05 mL/kg; one at peak stress followed by one at rest • Administer via a power injector at a flow rate of 4 mL/sec and follow each injection with a normal saline flush of 20 mL at same rate			
Dosage form and strength	Solution, gadoterate per mL: • 376.9 mg (0.5 mmol)	Solution, gadopiclenol per mL: • 485.1 mg (0.5 mmol)	Solution, gadoxetate per mL: • 181.43 mg (0.25 mmol)	Solution, gadobutrol per mL: • 604.72 mg (1 mmol)	Solution, gadobenate per mL: • 529 mg (0.5 mmol)	Solution, gadodiamide per mL: • 287 mg (0.5 mmol)	Solution, gadoteridol per mL: • 279.3 mg (0.5 mmol)
Boxed warning	GBCAs increase the risk for NSF among patients with impaired elimination of drugs. Avoid use in these patients unless diagnostic information is essential and not available with non-contrasted MRI or other modalities. Risk for NSF appears highest among patients with AKI or severe, CKD (GFR < 30 mL/min/1.73m^2). Screen patients for AKI and other conditions that may reduce renal function.						
	--	--	--	--	--	Not for intrathecal use	--
Contraindications	History of severe hypersensitivity to gadoterate	History of hypersensitivity reactions to gadopiclenol	History of severe hypersensitivity to gadoxetate	History of severe hypersensitivity to gadobutrol	History of hypersensitivity to GBCAs	• Patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2) or AKI • Prior hypersensitivity	History of hypersensitivity to gadoteridol

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Warnings/precautions	• NSF has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeated dosing appears to increase the risk. • Anaphylactic and other hypersensitivity reactions with cardiovascular, respiratory, or cutaneous manifestations, ranging from mild to severe, including death, have occurred. Monitor closely during and after administration. • Gadolinium is retained for months or years in brain, bone, and other organs. • ARF requiring dialysis has occurred in patients with chronic renal impairment and use of some GBCAs. • Extravasation may result in moderate irritation.						
	--	--	Serum iron determination using complexometric methods may result in falsely high or low values for up to 24 h after examination	• May overestimate the extent of malignancy in diseased breast in up to 50% of patients • Due to low sensitivity, a negative MRA study alone should not be used to rule out significant arterial stenosis	Cardiac arrhythmias have been observed in patients in clinical trials; assess patients for underlying conditions	• Inadvertent intrathecal use has caused convulsions, coma, sensory, and motor neurologic deficits • May interfere with serum calcium measurements with some colorimetric methods, resulting in serum calcium concentrations lower than true values.	--
					Certain lesions on non-contrast images may not be seen on contrast images. Exercise caution when interpreting contrast MR images in absence of companion non-contrast MR images		
Adverse reactions	(≥ 0.2%): Nausea, headache, injection site pain, injection site coldness, and rash	(≥ 0.2%): Injection site pain, headache, nausea, injection site warm and coldness, dizziness, and localized swelling	(≥ 0.5%): Nausea, headache, feeling hot, dizziness, and back pain	(≥ 0.5%): Headache, nausea, and dizziness	(> 1%): Nausea and headache	(≤ 3%): Nausea, headache, and dizziness	(≥ 0.9%): Nausea and taste perversion
ACR category for NSF[b]	Group II	Group II	Group III	Group II	Group II	Group I	Group II

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Drug interactions	Specific drug interaction studies have not been performed	Not reported	Not reported	Not reported	• May compete for the canalicular multispecific organic anion transporter • May prolong systemic exposure of drugs such as cisplatin, anthracyclines, vinca alkaloids, methotrexate, etoposide, tamoxifen, and paclitaxel	Specific drug interaction studies have not been performed	Not reported
Laboratory interactions	--	--	Serum iron determination using complexometric methods may result in falsely high or low values for up to 24 h after examination	--	--	May interfere with serum calcium measurements with some colorimetric methods, resulting in serum concentrations lower than true values. In patients with normal renal function, effect lasts 12 to 24 h	--
Pharmacology	Gadolinium is a paramagnetic molecule that develops a paramagnetic moment when placed in a magnetic field. The magnetic moment enhances the relaxation rates of water protons, leading to an increase in signal intensity.						
Physicochemical properties							
Structure	Macrocyclic	Macrocyclic	Linear	Macrocyclic	Linear	Linear	Macrocyclic
Ionicity	Ionic	Nonionic	Ionic	Nonionic	Ionic	Nonionic	Nonionic
Viscosity at 25°C (37°C), mPas[b]	3.4 (2.4)	12.6 (7.6)	-- (1.19)	-- (4.96)	9.2 (5.3)	2.0 (1.4)	2.0 (1.3)
Relaxivity 1.5T (3T) L x mmol^{-1} x sec^{-1} [serum]^2	3.6 (3.5)	12.8 (11.6)	6.9 (6.2)	5.2 (5)	6.3 (5.5)	4.3 (4)	4.1 (3.7)
Osmolality, mOsm/kg H_2O[2]	1350	850	688	1603	1970	789	630
Log K Therm (cond7.4)[2]	25.6 (19.3)	18.7	23.5 (18.7)	21.8 (15.5)	22.6 (18.4)	16.9 (14.9)	23.8 (17.2)

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Pharmacokinetics							
Protein binding	None	≤ 1.8%	Transient, < 10%	None	Transient	None	Unknown
Metabolism	None	None	None	None	None	None	Unknown
Elimination half-life (adults)	Female: 1.4 ± 0.2 h Male: 2.0 ± 0.7 h	1.5 h	0.91-0.95 h	1.8 h	1.17 ± 0.26-2.02 ± 0.6 h	77.8 ± 16 min	1.57 ± 0.08 h
Elimination half-life (adults, renal impairment)	Moderate: 5.1 ± 1 h Severe: 13.9 ± 1.2 h	Moderate: 3.8 h Severe: 11.7 h	--	Moderate: 5.8 ± 2.4 h Severe: 17.6 ± 6.2 h	Moderate: 6.1 ± 3 h Severe: 9.5 ± 3.1 h	--	Moderate: 10.65 ± 0.06 h Severe: 9.1 ± 0.26 h
Dissociation half-life (chelate)[3]	> 1 mo	Not reported	Not reported	Not reported	Not reported	35 sec	3 h
Route of elimination	Renal	Renal (98%)	Renal (50%) Hepatobiliary (50%)	Renal	Renal (78-96%) Hepatobiliary (0.6-4%)	Renal	Renal
Storage	25° C, excursions permitted to 15-30° C	25° C, excursions permitted to 15-30° C	25° C, excursions permitted to 15-30° C	25° C, excursions permitted to 15-30° C	25° C, excursions permitted to 15-30° C	20-25° C, excursions permitted to 15-30° C	25° C, excursions permitted to 15-30° C
How supplied[4]	Dotarem **Single-dose, glass vials** • 5 mL, 10 mL, 15 mL, 20 mL **Prefilled glass syringes** • 10 mL, 15 mL, 20 mL **Pharmacy bulk package vials** • 100 mL vials containing 100 mL of solution Clariscan **Single-dose, glass vials**	Elucirem **Single-dose, glass vials** • 3 mL, 7.5 mL, 10 mL, 15 mL **Single-dose, prefilled plastic syringes** • 7.5 mL, 10 mL, 15 mL **Pharmacy bulk package glass** • 30 mL, 50 mL, 100 mL Vueway **Single-dose, glass vials** • 3 mL, 7.5 mL, 10 mL,15 mL* **Single-dose, prefilled plastic syringes***	**Single-dose vials** • 10 mL,15 mL	**Single-dose vials** • 2 mL, 7.5 mL, 10 mL, 15 mL **Single-use, prefilled syringes** • 7.5 mL, 10 mL, 15 mL **Pharmacy bulk package vials** • 30 mL, 65 mL* *MEDRAD Imaging Bulk Package Transfer Spike	**Single-dose vials** • 5 mL, 10 mL, 15 mL, 20 mL **Pharmacy bulk package vials** • 50 mL,100 mL	**Single-dose glass vials** • 5 mL in 10 mL, 10 mL, 15 mL in 20 mL, and 20 mL **Single-dose, prefilled syringes*** • 10 mL in 20 mL, 15 mL in 20 mL, and 20 mL **Single-dose, Prefill Plus Easy Delivery System*** • 15 mL in 20 mL and 20 mL **Pharmacy bulk package polymer bottle** • 100 mL	**Single-dose vials** • 5 mL, 10 mL, 15 mL, 20 mL **Single-dose, prefilled syringes** • 10 mL,17 mL **Pharmacy bulk package vials** • 50 mL

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	• 5 mL, 10 mL, 15 mL, 20 mL **Prefilled glass syringes** • 10 mL in 20 mL, 15 mL in 20 mL, 20 mL in 20 mL **Pharmacy bulk polymer bottle** • 100 mL Gadoterate: **Single-dose, glass vials** • 5 mL, 10 mL, 15 mL, 20 mL **Pharmacy bulk package vials** • 100 mL	• 7.5 mL, 10 mL, 15 mL **Pharmacy bulk package glass** • 30 mL, 50 mL*, 100 mL* *Presentations may not be commercially available				*Presentations may not be commercially available	

Evidence summary	**Introduction**: Currently 7 approved GBCAs (10 products) are marketed in the US as MRI contrast agents. Gadoterate is supplied as 3 different products, including a branded product (Dotarem, Guerbet) and 2 bioequivalent, generic products (Clariscan, GE; gadoterate, Fresenius Kabi). Gadopiclenol was co-developed by Bracco and Guerbet and each company is commercializing the product independently under different brand names (Elucirem, Guerbet; Vueway, Bracco).[5] All the GBCAs share a common structure that consists of a gadolinium ion chelated to an organic ligand. The gadolinium-organic ligand complex improves the stability and safety of gadolinium. In addition to a common structure, all the GBCAs also have the same mechanism of action – namely altering the local magnetic environment of water protons in adjacent tissues, which shortens the intrinsic tissue T1 and T2 relaxation times. This relaxation is observed as a change in signal intensity on T1- or T2/T2*-weighted sequences.[2] The GBCA agents are differentiated by chelate structure, gadolinium-chelate stability, viscosity, ionicity, osmolality, volume of distribution, and relaxivity. Properties such as chelate structure, thermodynamic and kinetic stability, viscosity, ionicity, and osmolality mainly impact GBCAs' safety profile.[6] Based on the chemical structure of the chelating ligand, GBCAs are divided into 2 distinct structural classes: macrocyclic ligands bind the gadolinium ion in a cage structure and linear ligands bind the gadolinium ion in a chain structure. Within each structural class, there are ionic and nonionic GBCAs.[2,6,7] In general, macrocyclic complexes are the most stable and nonionic linear complexes the least.[2,3] As discussed in detail in the safety summary, the prevailing theory is that the stability of the gadolinium-chelate complex is a major factor in the development of NSF. In addition, the stability of the gadolinium-chelate may also be a major determinate for the deposition of non-chelated gadolinium in the brain and other tissues.[8] Similar to the iodinated contrast agents, there is a significant range in the viscosity and osmolality of the GBCAs; however, unlike iodinated contrast agents, differences in these physical properties are less impactful due to the smaller volumes of GBCAs typically administered and the slower injection flow rates.[2] Differences in volume of distribution, relaxivity, and concentration may impact the tissue enhancement of the various GBCAs. Six of the marketed GBCAs (Dotarem, Elucirem, Gadavist, Omniscan, ProHance, Vueway) are classified as pure extracellular agents because they rapidly distribute into the extracellular-extravascular space. All of the extracellular agents are exclusively eliminated through passive glomerular filtration.[6] Two GBCAs (Eovist and MultiHance) are taken up by hepatocytes and are variably eliminated through the hepatobiliary route, thus giving these agents some advantage for liver imaging.[6] While MultiHance acts as a dual extracellular and hepatic agent because of its minimal hepatic uptake and elimination (up to 4%), Eovist's application is limited to liver imaging because of its more extensive hepatic uptake and elimination (up to 50%).[7] Differences in relaxivity contribute to differences in signal-intensity enhancement or loss with greater relaxivity

values associated with higher signal-intensity enhancement on T1-weighted images and higher signal-intensity loss on T2-and T2*-weighted images. Excluding the hepatic agent Eovist, gadopiclenol (Elucirem, Vueway) has almost 2-fold greater relaxivity compared to the high-relaxivity agent, MultiHance and a relaxivity of 3 to 4 times that of conventional GBCAs.[2] MultiHance achieves its greater relaxivity through transient binding with albumin.[7] In contrast, gadopiclenol achieves greater relaxivity through water exchange kinetics, binding to 2 water nuclei (vs to 1 water nuclei for all other GBCAs). Interaction with a greater number of water molecules results in higher relaxivity.[9] All agents except for Gadavist are formulated at a standard 0.5 molar concentration; Gadavist is formulated at a higher 1.0 molar concentration. Due to its 2-fold higher concentration, Gadavist can be administered at half the injection volume compared with equimolar doses of standard 0.5 molar concentration GBCAs. Theoretically, a smaller, more concentrated bolus may confer an advantage in dynamic imaging applications.[7,10]

Although the GBCAs are FDA-approved for various indications, the extracellular GBCAs are viewed as mostly interchangeable from an efficacy perspective and off-label use is common.[6] The following discussion focuses on comparative efficacy for CNS imaging and for applications that a higher relaxivity and/or higher concentration may confer a benefit. The hepatic-specific agent, Eovist and GBCAs that have been withdrawn from the market are not discussed in this document.

Efficacy, conventional (static) CNS imaging: Based on an FDA review in 2016, the most frequent imaging performed on adult patients billed for an MRI/MRA procedure with a GBCA was for imaging of the head and non-extremities; for pediatric patients, the most common billed procedure was for imaging of the head.[11] All of the extracellular agents and MultiHance are FDA-approved for contrast-enhanced, MRI of the CNS. Because all extracellular GBCAs are approved for CNS imaging, there are multiple head-to-head comparisons. Results from several intraindividual crossover comparisons are summarized in Appendix A. Results from intraindividual comparisons are preferentially highlighted over interindividual, parallel comparisons because the former study design minimizes the confounding effects of patient-, disease-, and exam-related factors.

For the recently approved GBCA, gadopiclenol (Elucirem, Vueway), Guerbet and Bracco chose to pursue approval based on a demonstration of noninferiority of gadopiclenol given at half dose to Gadavist given at standard dose with the goal of reducing patient exposure to gadolinium. If given at an equivalent dose to Gadavist, gadopiclenol, with its greater than 2-fold higher relaxivity, would be expected to provide greater signal intensity; however, approval studies were not designed to demonstrate superiority. The primary objective of the pivotal phase 3 trial conducted in patients with CNS lesions was to demonstrate superiority of contrast enhanced to unenhanced MRI and the secondary objective was to demonstrate the noninferiority of gadopiclenol at half dose (0.05 mmol/kg) compared to standard-dose Gadavist (0.1 mmol/kg).[12] For both primary and secondary objectives, 3 co-primary endpoints related to lesion visualization were selected – border delineation, internal morphology, and degree of contrast enhancement – and rated on an ordinal scale by 3 independent readers. For all co-primary endpoints, all 3 readers rated paired pre- and post-contrast imaging with gadopiclenol superior to pre-contrast imaging, with post-contrast lesion visualization scores increased by over 95% compared to pre-contrast scores for all readers, thus the study met its pre-defined success criterion. For the secondary objective of noninferiority to Gadavist, a noninferiority margin of 10% was selected with the assumption that a difference of 0.35 for the mean lesion visualization score (mean assumed to be 3.5) would be clinically unimportant. It is important to note that the 3 co-primary lesion visualization endpoints are qualitative and are not validated against a reference standard; therefore, it is unknown if a 10% decrement in lesion visualization score is clinically unimportant. For all 3 readers, differences in the mean scores for lesion visualization endpoints between gadopiclenol and Gadavist were close to 0 and the lower bound of all 95% confidence intervals were above the noninferiority margin, suggesting that half-dose gadopiclenol is noninferior to standard-dose Gadavist. For the slight majority of images, readers preferred gadopiclenol to Gadavist (44.8%, 54.4%, and 57.3% of images); for the remainder of images, readers expressed either no preference or a preference for Gadavist. Despite a marginal preference for gadopiclenol, a change in treatment plan from pre-contrast to post-contrast MRI was similar between gadopiclenol (23.3% of patients) and Gadavist (23.7%). Likewise, there was no significant difference between GBCA agents in proposed therapeutic management of the CNS lesion.[12] Results from a phase 2b study[13] against the higher relaxivity agent, MultiHance were comparable to the results observed against Gadavist, namely that there were no significant differences between gadopiclenol 0.05 mmol/kg and MultiHance 0.1 mmol/kg for quantitative and qualitative evaluations. At equivalent dosing of 0.1 mmol/kg, the magnitude of the CNR was 32% to 45% higher with gadopiclenol than MultiHance, but this difference did not consistently translate to significantly higher mean scores for lesion visualization outcomes (lesion border delineation, visualization of lesion internal morphology, and lesion contrast enhancement) in favor of gadopiclenol across the 3 readers. The study may have been underpowered to demonstrate differences for this endpoint.

The high relaxivity, standard concentration agent MultiHance has been compared with standard relaxivity/standard concentration agents (Dotarem, Omniscan) and with the high concentration agent, Gadavist. Findings from the 3 largest comparisons that evaluated MultiHance against Dotarem (Benefit study),[14] Omniscan (MR-Enhance study),[15] and Gadavist (Merit study)[16] demonstrated a significant preference for MultiHance for all qualitative endpoints, including the primary endpoint of overall global diagnostic preference. For images where a preference was expressed for MultiHance, the primary reasons were superior contrast enhancement and better lesion delineation.[15,16] In addition to qualitative endpoints, quantitative endpoints were superior with MultiHance. Across the studies, MultiHance was associated with an approximately 20% to 30% increase in lesion enhancement compared with standard relaxivity comparators.[14-16] While results support that MultiHance produces significantly greater signal intensity enhancement, there is little evidence to directly link greater signal intensity enhancement with improved lesion detection, patient management, or surgical planning. Theoretically, superior contrast enhancement and lesion delineation should lead to better definition of resection and/or radiosurgical margins.

The high concentration agent Gadavist has been compared with standard relaxivity/standard concentration agents (Dotarem, ProHance) in multiple studies.[17-21] Findings from studies are mixed about the superiority of Gadavist over standard concentration agents. Results from comparisons that evaluated the agents at equimolar doses are briefly discussed. One study did not conduct inferential statistics for the comparison of Gadavist and ProHance at equimolar doses; therefore, the results of the study are included in Appendix 1, but not summarized here.[21] Of the 3 studies

	that compared Gadavist with a standard relaxivity/standard concentration agent at an equimolar dose, findings from a single study demonstrated that Gadavist was preferred over Dotarem by 2 of 3 readers overall.[18] For secondary diagnostic endpoints, readers expressed no significant preference for either agent for lesion delineation and only 1 of 3 readers expressed a preference for Gadavist for internal structure. All 3 readers preferred Gadavist to Dotarem for intensity of lesion enhancement, which is not an unexpected result given the slight differences in the agents' respective r1 relaxivities. Despite a preference for Gadavist for some of the qualitative endpoints, the difference between Gadavist and Dotarem for percent lesion enhancement was only 10% and did not translate to a significant difference between agents for CNR.[18] Additionally, there was no difference between agents in the number of lesions detected, suggesting that differences between the agents in lesion enhancement may have been statistically, but not clinically significant. In the remaining 2 studies, there was either no preference for Gadavist versus the comparator for the primary and secondary qualitative endpoints[19] or the comparator was noninferior to Gadavist for overall visualization and characterization.[17] Collectively, results of GBCA comparisons in the setting of conventional (static) contrast-enhanced MRI of the CNS suggest that r1 relaxivity (vs concentration) is the main determinant of signal enhancement and contrast efficacy. Imaging in the CNS setting typically occurs 3 to 5 minutes after GBCA administration at which time equilibration has already occurred; therefore, the concentration of gadolinium is irrelevant if GBCAs are administered at equivalent FDA-approved doses.[7] Results from head-to-head comparisons suggest that agents with greater relaxivities are associated with improvements in quantitative and qualitative endpoints, but these endpoints are surrogates. It is uncertain if improvements in conspicuity are associated with better patient management and improved clinical outcomes. Gadopiclenol was studied and is approved at half the dose of other GBCAs because of its greater relaxivity relative to other GBCAs. The reduction in gadolinium dose is theoretically beneficial, but it is unknown if gadopiclenol further reduces the already low risk of NSF and gadolinium retention that occurs with group II GBCA agents. **Efficacy, conventional (static) body imaging**: The use of gadopiclenol with MRI to detect and visualize lesions with abnormal vascularity in the body is briefly discussed because gadopiclenol is the first GBCA to be broadly approved to visualize lesions located throughout the body, including a first in class approval for visualization of musculoskeletal lesions. While Omniscan has the next broadest indication for visualization of non-CNS lesions, including lesions in the thorax, abdomen, and pelvis, it is a linear GBCA and utilization is minimal; therefore, gadopiclenol is the first macrocyclic GBCA that is broadly approved to visualize lesions located throughout the body. The macrocyclic agents ProHance and Gadavist have limited indications for visualization of non-CNS lesions (head/neck and breast, respectively); however, it is not uncommon in practice for extracellular GBCA agents to be used off-label for visualization of non-CNS lesions. The pivotal phase 3 trial[22] for approval of non-CNS lesion visualization was designed similarly to that of the phase 3 trial for CNS lesion visualization, namely the primary goal was to establish the superiority of paired pre- and post-contrast imaging with gadopiclenol to pre-contrast imaging for the 3 co-primary lesion visualization endpoints of border delineation, internal morphology, and degree of contrast enhancement. The secondary objective was to evaluate the noninferiority of half-dose gadopiclenol to that of standard-dose Gadavist for the 3 co-primary lesion visualization endpoints. The majority of patients presented with lesions of the thorax (26%), abdomen (36%), and pelvis (22%). Only 8% of patients presented with musculoskeletal lesions. Because there were a set of 3 readers for each body region, 3 meta-readers were created by pooling 1 reader for each body region. Scores from the 3 meta-readers were used to assess the 3 co-primary lesion visualization endpoints. Superiority and noninferiority criteria were met for the primary and second objectives, respectively. Although superiority criteria were satisfied for the primary objective, there was variability in lesion visualization scores across the 3 meta-readers. One meta-reader did not consistently report improvements for the 3 co-primary lesion visualization endpoints between paired images and pre-contrast images at the patient level; however, the superiority criterion was satisfied because 2 of 3 meta-readers reported improvements in lesion visualization endpoint scores with paired images vs pre-contrast images for over 95% of images. Other findings of potential interest include reported differences in lesion visualization scores by body region. There was a trend for larger differences in lesion visualization scores between paired and pre-contrast images for the thorax compared to the abdomen and pelvis. Due to Gadavist's limited labeling in the US for breast lesion visualization, only patients with breast lesions were enrolled in the US and nearly all thoracic MRIs were performed for breast lesions. The finding of enhanced visualization in the thoracic region may be spurious, or it may indicate that gadopiclenol improves breast lesion visualization more than visualization of lesions in other body areas. There was also a trend for smaller differences in visualization lesion scores between paired and pre-contrast images for musculoskeletal lesions compared to other body regions.[22] It is unknown if these findings are clinically meaningful because of the subjective nature of the lesion visualization co-primary endpoints and the absence of a reference standard. While half-dose gadopiclenol was noninferior to standard-dose Gadavist, an effectiveness claim cannot be supported because Gadavist is not FDA approved for whole body visualization. Results are informational only. Gadopiclenol-enhanced images were preferred in 12 to 15% of images, Gadavist-enhanced images were preferred in 5 to 11% of images, and for the remainder, blinded readers expressed no preference between gadopiclenol or Gadavist-enhanced images. A similar proportion of local investigators reported a potential treatment change after enhancement with gadopiclenol or Gadavist. **Efficacy, dynamic imaging applications**: For many GBCAs, use for contrast-enhanced, dynamic phase imaging (as used in applications such as PWI and contrast-enhanced MRA) is an off-label use. In PWI, the main determinant of quality is the degree of signal intensity loss that is caused by the passage of the contrast agent bolus through the region of interest. The relative amount of signal intensity loss depends on type of MR sequence, dose, concentration, and relaxivity of the contrast agent.[10] A sufficient drop in signal intensity loss (>20%) may be achieved by use of a high concentration agent (eg, Gadavist) or by use of a high relaxivity agent (eg, MultiHance). It has been suggested that the lower injection volume of Gadavist may be associated with improved bolus geometry – a more well-defined bolus with a sharper peak – compared with standard concentration GBCAs. Results of an early intraindividual study in healthy volunteers that compared 1 molar with 0.5 molar GBCAs validated that the more highly concentrated Gadavist had a significantly smaller bolus width, a smaller mean peak time, a higher contrast and CNR between gray and white matter, and qualitatively better parametric maps.[23] In this study, both GBCAs were administered at a high dose of 0.3 mmol/kg body weight. In subsequent studies that compared Gadavist with MultiHance (standard concentration, high relaxivity) at a standard dose of 0.1 mmol/kg body weight in healthy volunteers, there were no differences between the agents for signal intensity loss,

bolus width, image quality, or perfusion maps at 1.5 T[24] or at 3 T.[25] Findings from the limited number of intraindividual comparisons for PWI suggest that with short injection times (< 5 seconds), bolus geometry is not impacted by concentration; therefore, Gadavist has not demonstrated benefit beyond that achieved with MultiHance for PWI.[7,10]

Similar to PWI, images in dynamic bolus contrast-enhanced MRA are acquired during the first pass of a GBCA through the vessels of interest; however, in contrast-enhanced MRA, the level of signal enhancement is dependent on the r1 value of the agent rather than the r2* value of the agent. The majority of intraindividual comparisons of the high relaxivity agent, MultiHance have compared a single 0.1 mmol/kg dose of Multihance with a single (0.1 mmol/kg) or double-dose (0.2 mmol/kg) of the standard relaxivity agent, Magnevist. Results have consistently demonstrated superiority of single-dose MultiHance versus single-dose Magnevist for qualitative and quantitative enhancement in various vascular territories at 1.5 T (peripheral arteries[26]; run off vessels[27]). In studies that assessed diagnostic performance, single-dose MultiHance was superior to single-dose Magnevist.[26] Significant differences in image quality and contrast enhancement in favor of MultiHance have also been shown at 3 T (supraortic vessels[28]). Based on multiple crossover studies in various vascular territories, double-dose Magnevist provides similar image quality and contrast enhancement as single-dose MultiHance at 1.5 T (renal arteries,[29] peripheral arteries,[30] and supra-aortic arteries[31]). The better imaging performance of MultiHance compared with Magnevist has been ascribed to the higher r1 of MultiHance.[7]

The reduced injection volume of Gadavist is assumed to facilitate a more compact bolus and increased intravascular concentration of gadolinium during arterial first pass, which should improve signal enhancement. However, data from studies that have compared Gadavist with standard concentration GBCAs at the same dose are equivocal about the superiority of Gadavist for dynamic MRA. Results of some studies suggest no significant differences between Gadavist and Magnevist for qualitative image quality,[32,33] quantitative measures (SNR and/or CNR)[32,34] or diagnostic accuracy[33] or between Gadavist and Dotarem for qualitative or quantitative measures.[35] Results of some studies suggest that Gadavist is superior to standard concentration GBCAs for signal enhancement (vs Magnevist for abdominal 3D MRA and vs Dotarem for lower limb MRA), but not for image quality or diagnostic confidence.[36,37] In a more recent comparison among Gadavist, Dotarem, and MultiHance that evaluated a total dose of 0.1 mmol/kg split 70% to 30% between static and dynamic MRA imaging, Gadavist had a significantly higher SNR compared with both comparators at the level of the proximal internal carotid artery in static and dynamic MR angiography and in the distal internal carotid artery at the level of the skull base in dynamic MRA. Despite differences among GBCAs for SNR, the calculation of vessel sharpness did not differ. Qualitative image quality was compared among the agents for static images only, results of which are likely not transferable to dynamic imaging quality.[38] Reasons for discordant results in the literature are unclear. It may be that differences are attributable to differences in examined vascular territory, varied study designs (intra vs interindividual design, healthy vs patients), and different MRA techniques. In a systematic review, the authors found that in MRA, non equimolar delivery rates favored Gadavist, but if adjusted and delivered at the same equimolar rate, advantages conferred by high concentration were removed.[39]

Safety, acute: The GBCAs are generally well tolerated during administration and are associated with a low occurrence of acute adverse events. Acute adverse events can be divided into those that are classified as nonallergic reactions (eg, headache, fatigue, arthralgia, taste perversion, flushed feeling, nausea, or vomiting) and those that are idiosyncratic, allergy-like reactions (eg, hives, diffuse erythema, respiratory distress, chest tightness, and periorbital edema). In publications, the incidence of acute reactions with the GBCAs has ranged from 0.06% to 0.3% with mild adverse reactions occurring more frequently than severe ones. In general, severe adverse reactions are more common in patients with a history of asthma or allergy, in patients who were administered a GBCA at a faster than recommended rate, and in patients with a history of hypersensitivity to a GBCA or to an iodinated contrast agent.[40,41] The incidence of acute adverse events does not appear to differ among the GBCAs based on safety results of intraindividual comparisons.

Safety, long-term (NSF): Long-term, GBCAs are associated with the development of NSF. Because the largest number of unconfounded cases of NSF have occurred after exposure to Omniscan (linear, nonionic), Magnevist (linear, ionic) and Optimark (linear, nonionic) and the fewest cases have occurred after exposure to Dotarem (macrocyclic, ionic), Gadavist (macrocyclic, nonionic), and ProHance (macrocyclic, nonionic), the prevailing theory is that the development of NSF in at-risk patients is inversely related to the stability of the gadolinium-chelate complex. Risk factors for the development of NSF include ESRD, severe CKD, and administration of high doses of GBCAs either through single or repeat administrations. Other risk factors or “co-factors/contributory factors” have been proposed, been causality has not been consistently confirmed. Since NSF has never been documented in a patient with normal renal function, it is proposed that the prolonged clearance of GBCAs in patients with renal insufficiency allows time for gadolinium to become dissociated or displaced from less stable complexes. Displaced gadolinium binds to anions, forming a precipitate that deposits in various tissues and causes a fibrotic response.[2,40]

The FDA required a boxed warning be added to the prescribing information of all GBCAs in 2006 to describe the relationship between GBCA administration and development of NSF. In 2010, the FDA revised prescribing information to recommend against use of the linear agents, Omniscan, Magnevist, and Optimark in patients with AKI or severe CKD (GFR < 30 mL/min/1.73m^2).[42] The ACR categorizes the GBCAs into 3 groups relative to each agent’s documented association with development of NSF and provides renal monitoring recommendations for each group. Group I agents (Omniscan, Magnevist, Optimark) are associated with the greatest number of NSF cases, group II agents (MultiHance, Gadavist, Dotarem, ProHance, Elucirem, and Vueway) are associated with few, if any, unconfounded cases of NSF, and group III agents (Eovist) have limited data regarding NSF risk, but few reports of unconfounded cases. The ACR strongly prefers use of group II agents in patients at risk for NSF. If group I or III agents are used in patients at risk for NSF, the ACR recommends that patients be informed about the potential risk and that the physician carefully balances the risks and benefits of performing a contrast-enhanced MRI.[2] Recommendations by the FDA, European Commission, and ACR to limit use of GBCAs in at-risk patients and to use agents that confer the lowest risk have almost eliminated new cases of NSF.

	Safety, long-term (Gadolinium deposition): In addition to NSF, multiple studies have shown evidence of residual tissue brightness in the deep nuclei of the brain, particularly in the globus pallidus and the dentate nucleus in patients that have undergone multiple GBCA-enhanced MRI exams.[2,8,11] The clinical significance of gadolinium deposition is unknown. No studies link gadolinium tissue deposition to the development of clinical syndromes other than NSF.[40] The deposition of gadolinium in the brain appears to be dose-related and is independent of renal function or BBB integrity. Data from human autopsy and rodent necropsy studies suggest that all of the GBCAs, regardless of structure or ionicity, are associated with some degree of residual gadolinium deposition after administration.[43-45] In adults, human[46-50] and animal research[51] suggest that residual gadolinium deposition is higher after administration of linear agents than after administration of macrocyclic agents based on T1 signal hyperintensity in the globus pallidus and dentate nucleus on unenhanced MRI.[11] Differences in the degree of gadolinium deposition also appear to exist within the linear class. Lower deposition has been reported with MultiHance compared with Omniscan or Magnevist[43,47,52] suggesting that agent specific characteristics, such as protein binding, may impact the degree of gadolinium deposition.[8] Results of pediatric studies largely mirror those of adults. Multiple pediatric studies have shown increased T1 signal intensity in the globus pallidus and dentate nucleus after multiple administrations of Magnevist or Omniscan.[45] In contrast, in the majority, but not all, multiple administrations of macrocyclic agents (Dotarem, Gadavist, ProHance) have not been associated with increased T1 signal intensities.[45] Results of 2 studies that retrospectively evaluated multiple administrations of Dotarem have shown increases in measured signal intensity ratios compared with an age-matched cohort.[53,54] In 1 of the 2 studies, this increase was not associated with visible T1 hyperintensity.[53] It is unclear if any macrocyclic agent is superior to another; however, results of an animal study that compared Dotarem, Gadavist, and ProHance suggested that Dotarem (ionic, macrocyclic) is cleared faster from the brain than the others based on significantly lower concentrations of gadolinium in the cerebrum, cerebellum, femur and renal tissues in rats that received Dotarem.[45] Results from imaging studies in rats suggest that the newest macrocyclic agent, gadopiclenol (nonionic) has similar in vivo distribution and washout behavior as other macrocyclic agents when given at equimolar doses.[55,56] After single and repeat injections, gadopiclenol was not associated with T1 hyperintensity in the dentate nucleus.[55] In comparison, the active linear comparators, MultiHance and Omniscan were associated with T1 hyperintensity while the active macrocyclic comparator, Gadavist was not.[55] Gadolinium concentrations were significantly lower 1 month after administration of the 20th dose of gadopiclenol (vs. MultiHance) in the tissues of the cerebellum, the cortical brain, the subcortical brain, and in the muscle; however, gadolinium was still detectable.[56] Following single-dose administration of gadopiclenol or Gadavist at an equimolar dose, gadolinium concentrations decreased by 80% during a 12-month washout period.[55] There was no evidence to suggest that gadolinium became bound to macromolecules during this washout period, suggesting both macrocyclic agents have high kinetic inertness. In contrast, Omniscan was associated with a 15% decrease in gadolinium concentration over the same period with evidence that gadolinium was bound to macromolecules.[55] Between 2015 and 2017, the FDA released 3 safety communications about brain retention of GBCAs.[57-59] In the third safety communication, the FDA concluded that the benefits of GBCAs still outweigh their risks; however, the agency recommended that health care professionals consider the gadolinium retention characteristics of specific agents in patients that are at higher risk of retention, including patients requiring multiple GBCA-enhanced exams, pregnant women, pediatrics, and patients with inflammatory conditions. According to FDA guidance, all GBCAs have been associated with gadolinium retention, but gadolinium levels remaining in the body are the highest after certain linear agent use (Omniscan and Optimark) and lowest after macrocyclic agent use (Dotarem, Gadavist, and Prohance).[59] In 2017, the European Commission also concluded that gadolinium deposition in the brain had not been associated with adverse health effects, but suspended the marketing authorization for IV Omniscan, Optimark, and Magnevist and restricted the use of IV MultiHance to liver scans.[60] The FDA has requested that additional research be conducted to better understand the mechanism of deposition, the chelation state of deposited gadolinium, and the toxicity of deposited gadolinium.[2,11] Both the ACR and International Society of Magnetic Resonance in Medicine suggest that when selecting a GBCA, many factors should be considered, including pharmacokinetics, relaxivity, efficacy, potential adverse events, patient age, probability of the need for repeated examinations, cost, and the propensity of an agent to deposit gadolinium.[2,8] As a result of the continued uncertainty about the toxicity of residual gadolinium, many facilities have adopted policies that encourage the use of a macrocyclic agent and reserve use of linear agents for patients that have a documented sensitivity to macrocyclic agents.[3]

Abbreviations: ACR = American College of Radiology; AKI = acute kidney injury; ARF = acute renal failure; BBB = blood brain barrier; CAD = coronary artery disease; CKD = chronic kidney disease; CNR = contrast-to-noise ratio; CNS = central nervous system; FDA = Food and Drug Administration; GBCA = gadolinium based contrast agent; GFR = glomerular filtration rate; IV = intravenous; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; NR = not reported; NSF = nephrogenic systemic fibrosis; PWI = perfusion weighted imaging; SNR = signal-to-noise ratio; T = tesla

[a] Data obtained from IQVIA[1]

[b] Group I agents: Patients receiving group I GBCAs should be considered at risk of developing NSF if any of the following conditions apply to the patient: on dialysis (any form), severe or end-stage CKD without dialysis, or AKI; Group II agents: The risk of NSF among patients exposed to standard or lower than standard doses of group II GBCAs is sufficiently low or possibly nonexistent such that assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration; Group III agents: There is insufficient real-life data to determine the risk of NSF from administration of group III agents, thus it is important to identify patients at risk of developing NSF prior to injection of group III GBCAs.[2]

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Appendix A: Intraindividual comparisons – CNS imaging

Study	Design	Patients	Treatment	Procedure	Evaluation	Outcomes
Invest Radiol. 2023;58:307-313 (PICTURE study)	MC, DB, R, 2-sequence, 2-period, crossover, superiority (non-enhanced) and noninferiority (vs. Gadavist)	• Patients with known or highly suspected CNS lesions based on results of a previous imaging procedure • Patients with eGFR < 30 mL/min/1.73 m^2 were excluded	Patients received both Gadavist and Elucirem in random order, separated by 2-14 d. MRI was performed before and after each contrast agent (n = 256) • **Gadavist** 0.1 mmol/kg • **Elucirem / Vueway** 0.05 mmol/kg	MRI performed on 1.5 T systems (n = 109 patients) and 3 T systems (n = 130 patients)	3 independent, blinded readers • Border delineation – distinction of the lesion from surrounding tissues, structures, or edema and the detection of the extent of the lesion: 4-point scale (1 = none to 4 = excellent) • Internal morphology – identification of lesion architecture and intra-lesion features (4-point scale (1 = poor to 4 = excellent) • Degree of contrast enhancement – qualitative assessment: 4-point scale (1 = none to 4 = excellent)	Primary: Paired pre- and post-contrast imaging with Elucirem/Vueway is superior to pre-contrast imaging for the 3 co-primary endpoints (n = 239). To conclude superiority, difference in mean scores (95% CI) had to be greater than 0 for at least 2 of the 3 readers for all 3 co-primary endpoints. Superiority criteria were met. Secondary: Paired pre- and post-contrast imaging with Elucirem/Vueway is non-inferior to paired imaging with Gadavist for the 3 co-primary endpoints. NIM of 10% difference in visualization score was selected (n = 236). Difference in mean scores (95% CI) Border delineation • Reader 1: -0.02 (-0.06 to 0.02) • Reader 2: 0.03 (-0.04 to 0.11) • Reader 3: 0.02 (1-0.01 to 0.05) Internal Morphology • Reader 1: -0.01 (-0.04 to 0.03) • Reader 2: 0.02 (-0.05 to 0.09) • Reader 3: 0.05 (0.01 to 0.08) Degree of contrast enhancement • Reader 1: 0.01 (-0.04 to 0.07) • Reader 2: 0.05 (-0.03 to 0.12) • Reader 3: 0.09 (0.03 to 0.15) Preference for Elucirem/Vueway (vs. Gadavist preference) • Reader 1: 44.8% (14.5%) • Reader 2: 54.4% (24.1%) • Reader 3: 57.3% (19.5%)

Study	Design	Patients	Treatment	Procedure	Evaluation	Outcomes
Am J Neuroradiol. 2017;38 (9):1681-1688. (REMIND study)	MC, DB, R, intraindividual, 2-sequence, 2-period, crossover noninferiority study	• Patients with known or highly suspected primary brain (intracranial) tumors detected by previous CT or MRI • Patients with eGFR < 30 mL/min/1.73m^2 were excluded	Each patient underwent 2 identical MRI examinations with a minimum of 48 h between exams (n = 268) • **Dotarem** 0.1 mmol/kg (0.2 mL/kg) • **Gadavist** 0.1 mmol/kg (0.1 mL/kg)	MRI performed on 1.5 T systems (n = 15 centers) and 3 T systems (n = 12 centers) Postcontrast T1-weighted imaging initiated 5 ± 1 min after injection	3 independent, blinded readers • Overall visualization and characterization of lesion: 4-point scale (0 = poor to 3 = excellent)[a] • Diagnostic confidence: 5-point scale (1 = nil (0-4% confidence) to 5 = excellent (96-100% confidence)) • Border delineation and internal morphology: 3-point scale (0 = unevaluable to 2 = seen completely/perfectly) • Degree of contrast enhancement: 3-point scale (0 = nil to 2 = strong enhancement)	Per-protocol set (n = 234) NIM: -10% Difference in the percentage of images rated as good or excellent for overall lesion visualization and characterization (Dotarem minus Gadavist) • Reader 1: 2.3% (95% CI, -1.3-5.9) • Reader 2: -2.5% (95% CI, -6.5-1.4) • Reader 3: Not statistically evaluable Border delineation (based on sum of scores) • Reader 1: No preference: 67.5%; Dotarem: 16.5%; Gadavist: 16% • Reader 2: No preference: 67.8%; Dotarem: 15.5%; Gadavist: 16.7% • Reader 3: No preference: 82.8%; Dotarem: 6.5%; Gadavist: 10.8% Internal morphology (based on sum of scores) • Reader 1: No preference: 86.1%; Dotarem: 8.2%; Gadavist: 5.6% • Reader 2: No preference: 76.8%; Dotarem: 10.3%; Gadavist: 12.9% • Reader 3: No preference: 88.4%; Dotarem: 10.3%; Gadavist: 12.9% Contrast enhancement (based on sum of scores) • Reader 1: No preference: 81.8% • Reader 2: No preference: 85.8% • Reader 3: No preference: 88.5% Diagnostic confidence: Results not provided, but reported not to be different

Study	Design	Patients	Treatment	Procedure	Evaluation	Outcomes
Eur J Radiol. 2013;82(1):139-145.	MC, single-blind, R, intraindividual, crossover	• Patients with known cerebral intra axial or extra axial neoplastic lesions	Each patient underwent 2 identical MRI examinations with a minimum of 48 h between exams (n = 151) • **Dotarem** 0.1 mmol/kg • **Gadavist** 0.1 mmol/kg	MRI performed on 1.0 T systems (21% of patients) or 1.5 T systems (79% of patients)	3 independent, blinded readers • Overall preference: (1 = Gadavist, 0 = no preference; -1 = Dotarem preference)[a] • Intensity of lesion enhancement, lesion delineation from its surrounding tissue, internal lesion structure: assessed on same scale as above	Per-protocol set (n = 133) Overall preference • No preference was excluded in analysis, which was the largest % for some readers • Across all readers, when a preference was stated, Gadavist was preferred: 66% (95% CI, 57-74%) (*P* = .0007) • 2 of 3 readers significantly preferred Gadavist Intensity of lesion enhancement • No preference was excluded in analysis • Significant preference for Gadavist for all 3 readers Lesion delineation • No preference was excluded in analysis • No significant differences for any readers Internal structure • No preference was excluded in analysis • Significant preference for Gadavist by single reader
Neuroradiology. 2004;46(8):655-665.	MC, DB, R, intraindividual, crossover	• Patients with suspected brain metastases or glioma	Each patient underwent 2 identical MRI examinations with a minimum of 48 h between exams (n = 31) • **Dotarem** 0.1 mmol/kg • **MultiHance** 0.1 mmol/kg	MRI performed on 1.0 T (n = 23) and on 1.5 T (n = 8) systems?	2 independent, blinded readers • Overall assessment of contrast enhancement:[a]	Per-protocol set (n = 19) Overall assessment of contrast enhancement • Reader 1 ranked Multihance superior to Dotarem in 18 of 19 patients (*P* < .0001) • Reader 2 ranked Multihance superior to Dotarem in 15 of 21 patients (*P* = .005)

Study	Design	• Patients	Treatment	Procedure	Evaluation	Outcomes

Am J Neuroradiol. 2015;36(1):14-23.
 	
(TRUTH study)
	MC, DB, R, intraindividual, crossover	• Patients with known or suspected brain tumors	Each patient underwent 2 identical MRI examinations with a minimum of 48 h between exams (n = 229)
			
			• **Gadavist** 0.1 mmol/kg
			• **ProHance** 0.1 mmol/kg
				MRI performed on 1.5 T systems?.
				
				Image acquisition occurred within 3-10 mins after contrast
					3 independent, blinded readers
					
					• Diagnostic confidence score: (5 = single diagnosis, correctly matched to 1 = no match, nondiagnostic or no lesions detected at MRI)
					
					• Qualitative assessment: overall diagnostic preference[a] lesion border delineation, disease extent, visualization of lesion internal morphology, and lesion contrast enhancement compared with surrounding normal tissue (3-point scale: -1 = examination 1 superior to +1 = examination 2 superior).
						Noninferiority of Prohance to Gadavist assessed for overall diagnostic preference (n = 198)
						
						NIM: -5%
						
						Overall diagnostic preference
						• Results presented graphically
						• Reader 1, 2, and 3: No preference for either agent for overall diagnostic preference or for any of the qualitative assessments.
						• Lower limit of all 95% CI were greater than NIM
						
						Confidence for brain tumor diagnosis (n = 128)
						• Prohance vs. Gadavist
						  ○ Reader 1: 3.6 ± 1.8 vs. 3.3 ± 1.9 (*P* = .016)
						  ○ Reader 2: 3.6 ± 1.5 vs. 3.4 ± 1.6 (*P* = .011)
						  ○ Reader 3: 3.5 ± 1.6 vs. 3.3 ± 1.7 (*P* = .119)

Eur Radiol. 2013;23(12):3287-3295.	SC, OL, R, intraindividual, crossover	• Patients with known CNS lesions	Each patient underwent 2 identical MR imaging examinations within a minimum of 12 h between exams (n = 59) • **Gadavist** 0.1 mmol/kg • **ProHance** 0.1 mmol/kg	--	2 independent, blinded readers • Overall assessment of contrast enhancement[a]	Full analysis set (n = 51) Overall assessment of contrast enhancement preference • Reader: 1: Prohance: 32%; Gadavist: 68% (*P* = .0226) • Reader 2: Prohance: 18%; Gadavist: 68% (*P* = .0005) Overall preference for one or the other examination • Reader 1: Prohance: 29%; Gadavist: 71% (*P* = .0046) • Reader 2: Prohance: 18%; Gadavist: 67% (*P* = .0002)

Study	Design	• Patients	Treatment	Procedure	Evaluation	Outcomes
Am J Neuroradiol. 2012;33 (6):1050-1058. (MERIT study)	MC, DB, R, intraindividual, crossover study	• Patients with known or suspected brain tumors	Each patient underwent 2 identical MRI exams with a minimum of 48 h between exams (n = 122) • **Gadavist** 0.1 mmol/kg (0.1 mL/kg) • **MutiHance** 0.1 mmol/kg (0.2 mL/kg)	MRI performed on I.5 T systems 3D high-resolution T1 GRE acquisitions after injection	3 independent, blinded readers • Lesion border delineation, disease extent, visualization of lesion internal morphology, and lesion contrast enhancement: 3-point scale (-1 = examination 1 superior; 0 = examinations equal; +1 = examination 2 superior) • Superior was recorded if agent allowed for better separation of ≥ 1 lesion from surrounding tissue, structures, or edema; better definition of lesion extent; clearer depiction of intralesion features; better difference in SI between lesion and surrounding normal tissue; or depiction of ≥ 1 lesion only after that examination	No primary outcome identified *P* < .01 considered significant due to multiple comparisons Analysis set (n = 114) Global diagnostic preference: Multihance vs. Gadavist • Reader 1: 40.7% vs. 5.3%; *P* < .0001 • Reader 2: 47.4% vs. 6.1%; *P* < .0001 • Reader 3: 53.2% vs. 6.1%; *P* < .0001 Lesion border delineation preference: Multihance vs. Gadavist • Reader 1: 38.1% vs. 4.4%; *P* < .0001 • Reader 2: 34.2% vs. 2.6%; *P* <.0001 • Reader 3: 34% vs. 2.6%; *P* <.0001 Definition of disease extent preference: Multihance vs. Gadavist • Reader 1: 15.9% vs. 0.9%; *P* < .0001 • Reader 2: 18.4% vs. 2.6%; *P* < .0001 • Reader 3: 17.5% vs. 0%; *P* < .0001 Visualization of lesion internal morphology preference: Multihance vs. Gadavist • Reader 1: 34.5% vs. 4.4%; *P* < .0001 • Reader 2: 30.7% vs. 3.5%; *P* < .0001 • Reader 3: 31.6% vs. 0.9%; *P* < .0001 Lesion contrast enhancement preference: Multihance vs. Gadavist • Reader 1: 46.9% vs. 6.2%; *P* < .0001 • Reader 2: 54.4% vs. 8.8%; *P* < .0001 • Reader 3: 43.9% vs. 6.1%; *P* < .0001

Study	Design	• Patients	Treatment	Procedure	Evaluation	Outcomes
Am J Neuroradiol. 2015;36(9):1589-1598. (BENEFIT study)	MC, DB, R, intraindividual, crossover study	• Patients with known or suspected brain tumors	Each patient underwent 2 identical MRI exams with a minimum of 48 h between exams (n = 177) • Patients in Arm 1 received **Dotarem** and **MultiHance**, both administered at 0.1 mmol/kg • Patients in Arm 2 received **Dotarem** at 0.1 mmol/kg and **MultiHance** at 0.05 mmol/kg	MRI performed on I.5 T systems Postcontrast acquisition began at 3-10 min after injection	3 independent, blinded readers • Lesion border delineation, definition of extent of disease, visualization of lesion internal morphology, and lesion contrast enhancement: 3-point scale (-1 = exam 1 superior better, 0 = exams equal; 1 = exam 2 superior) • Superiority for 1 exam was recorded if: better separation of ≥ 1 lesion from surrounding tissue, structures or edema; better definition of lesion extent; clearer depiction of intralesion features; better contrast between lesions and surrounding normal tissue; or the ability to identify ≥ 1 lesion seen only on that examination	Superiority evaluated (Arm 1 (n = 63); Arm 2 (n = 96)) Global diagnostic preference, Arm 1 • Reader 1: Dotarem: 1.6%; Multihance: 49.2% (*P* < .0001) • Reader 2: Dotarem: 3.2%; Multihance: 82.3% (*P* < .0001) • Reader 3: Dotarem 3.2%; Multihance: 69.4% (*P* < .0001) Lesion border delineation preference, Arm 1 • All readers significantly preferred Multihance vs. Dotarem (40.3%-54.8% vs. 1.6%-3.2%) (*P* < .0001) Definition of disease extent • All readers significantly preferred Multihance vs. Dotarem (23.8%-29% vs. 0-3.2%) (*P* < .0001 for Readers 1 and 2) Visualization of lesion internal morphology • All readers significantly preferred Multihance vs. Dotarem (15.9%-37.1% vs. 0-1.6%) Lesion contrast enhancement • All readers significantly preferred Multihance vs. Dotarem (49.2%-82.3% vs. 1.6%-3.2%) Arm 2 – No significant differences between groups for any qualitative assessment

Study	Design	• Patients	Treatment	Procedure	Evaluation	Outcomes
Invest Radiol. 2011;46(7):411-418.	MC, single-blind, R, intraindividual, crossover, noninferiority study	• Patients, aged 20 years or older, with diagnosed primary cancer and known or suspected brain metastases	Each patient underwent 2 identical MRI exams within a minimum of 24 h between exams (n = 164) • **Gadavist** 0.1 mmol/kg and 0.2 mmol/kg • **ProHance** 0.2 mmol/kg	MRI performed on 1.5 T systems (n = 20 centers) and 3 T systems (other centers) Post-contrast imaging was started at 10 ± 1 min after the start of the first injection and 2-3 min after the start of the additional injection.	3 independent, blinded readers • Number of detected lesions[a] • Degree of contrast enhancement, border delineation: 4-point scale (1 = no to 4 = excellent) • Image permits treatment decision to be made: confident, not confident, or not assessable	Per-protocol (n =151) NIM: -1 Mean number of detected lesions per patient[a] • Gadavist 0.1 mmol/kg: 6.28 • Gadavist 0.2 mmol/kg: 6.92 • Prohance 0.2 mmol/kg: 6.87 Difference in lesion detection (Gadavist 0.1 mmol/kg - Prohance 0.2 mmol/kg: -0.58 (95% CI, -0.87 to -0.29) Difference in lesion detection (Gadavist 0.2 mmol/kg - Prohance 0.2 mmol/kg): 0.06 (95% CI, -0.23 to 0.36) Good or excellent contrast enhancement • No significant differences between agents for any of the 3 readers Good or excellent border delineation • Reader 1: Prohance 0.2 mmol/kg superior to Gadavist 0.1 mmol/kg (71.4% vs. 67.1%) Treatment planning • All enhanced images were rated as “confident” for treatment planning Patients selected for SRS therapy • Gadavist 0.1 mmol/kg vs. Prohance 0.2 mmol/kg: 36.9% of images were ranked as comparable for treatment decisions • Gadavist 0.2 mmol/kg vs. Prohance 0.2 mmol/kg: 48.4% of images were ranked as comparable for treatment decisions

Study	Design	• Patients	Treatment	Procedure	Evaluation	Outcomes
Am J Neuroradiol. 2008;29(9):1684-1691. (MR-ENHANCE study)	MC, DB, R, intraindividual, crossover study	• Patients with known or suggested brain tumors	Each patient underwent 2 identical MRI exams within a minimum of 48 h between exams (n = 136) • **Omniscan** 0.1 mmol/kg • **MultiHance** 0.1 mmol/kg	MRI performed on 1.5 T systems Postcontrast acquisition began at 3-10 min after injection	3 independent, blinded readers • Lesion border delineation, disease extent, visualization of lesion internal morphology, and lesion contrast enhancement compared with surround normal tissue: 3-point scale (-1 = exam 1 superior; 0 = exams equal; 1 = exam 2 superior) • Superiority for 1 exam was recorded if: better separation of ≥ 1 lesion from surrounding tissue, structures or edema; better definition of lesion extent; clearer depiction of intralesion features; better contrast between lesions and surrounding normal tissue; or the ability to identify ≥ 1 lesion seen only on that examination	Analysis set (n = 113) Superiority evaluated Global diagnostic preference • Reader 1: Multihance: 55.8% vs. Omniscan: 2.7% (*P* < .0001) • Reader 2: Multihance: 68.1% vs. Omniscan: 1.8% (*P* < .0001) • Reader 3: Multihance: 64.6% vs. Omniscan: 2.7% (*P* < .0001) Lesion border delineation, definition of disease extent, lesion internal morphology, lesion contrast enhancement • Results provided in graph format only • “Highly significant preference was demonstrated for each individual diagnostic information endpoint” Differences in lesion number detection were noted for 5 of 27 patients with metastases by 1 or more readers. In 3 of the 5 patients, the difference was not clinically relevant due to the large quantity of lesions.

Abbreviations: CI = confidence interval; CNS = central nervous system; CT = computed tomography; DB = double-blind; eGFR = estimated glomerular filtration rate; MC = multicenter; MRI = magnetic resonance imaging; NIM = noninferiority margin; OL = open label; R = randomized; SRS = stereotactic radiosurgery; T = tesla;

[a] Primary endpoint

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