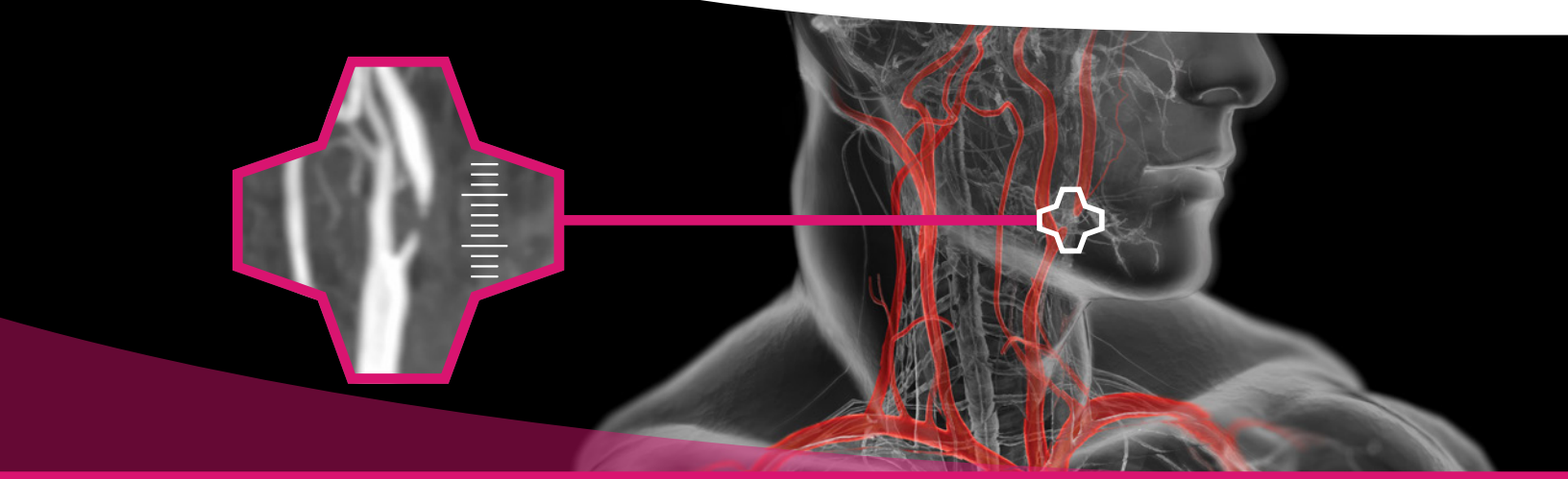


Seek the Details

Indications and Usage

Gadavist® (gadobutrol) injection is a gadolinium-based contrast agent indicated for use with magnetic resonance imaging (MRI):

- To detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system in adult and pediatric patients (including term neonates)
- To assess the presence and extent of malignant breast disease

Gadavist® is indicated for use in magnetic resonance angiography (MRA):

- To evaluate known or suspected supra-aortic or renal artery disease in adult and pediatric patients (including term neonates)

Important Safety Information

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk of NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or
  - Acute kidney injury
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended GADAVIST dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

Please see additional Important Safety Information throughout this piece.

Please click here to see the Gadavist® Full Prescribing Information (Vials & Syringes).

Please click here to see the Gadavist® Full Prescribing Information (Pharmacy Bulk Package).

Learn more about Gadavist at gadavist.com

Gadavist®
(gadobutrol) injection
1 mmol/mL

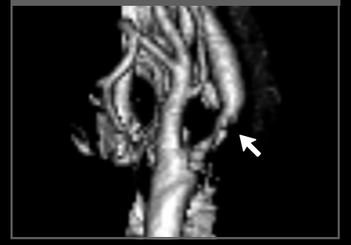
Compared to Unenhanced Magnetic Resonance Angiography (MRA):

See More With Gadavist

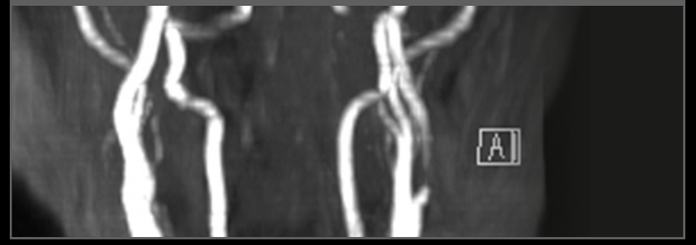
Case: Supra-aortic Magnetic Resonance Angiography

Patient History: 69-year-old Caucasian male with a history of hypertension, smoking, and recent stroke.

Computed Tomography Angiography (CTA)



Unenhanced 2D Time-of-Flight (ToF) MRA



Gadavist MRA Parameters

Parameter	Value
Plane	Coronal
Mode	3D
Pulse sequence (SPGR, T1FFE, FLASH, etc.)	Incoherent gradient echo (spoiled)
Timing	Fluoro triggered/ bolus tracking method
TE	2 ms
TR	4 ms
Flip angle	20–40 (25 preferred)
NEX	1.0
Matrix (frequency × phase)	512 × 256
Slice thickness	2 mm
Spacing	Overlap 1 suggested
Voxel size (coronal)	1.25 × 1.75 × 2.0 mm
k-space	Elliptical centric filling
Acceleration factor (iPAT, ASSET, SENSE, GRAPPA, etc.)	2–4

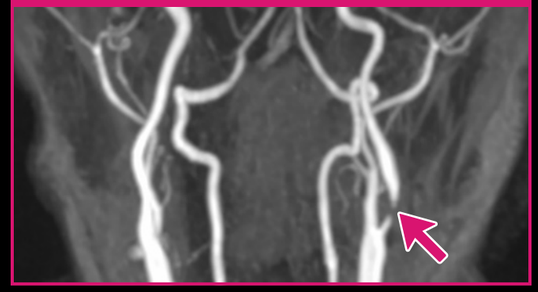
Important Safety Information (continued)

Contraindication and Important Information about Hypersensitivity Reactions: Gadavist® is contraindicated in patients with history of severe hypersensitivity reactions to Gadavist®. Anaphylactic and other hypersensitivity reactions with cardiovascular, respiratory, or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred following Gadavist® administration. Before Gadavist® administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Gadavist®.

Please see additional Important Safety Information throughout this piece.

Case Source, Gadavist Phase III Clinical Trial

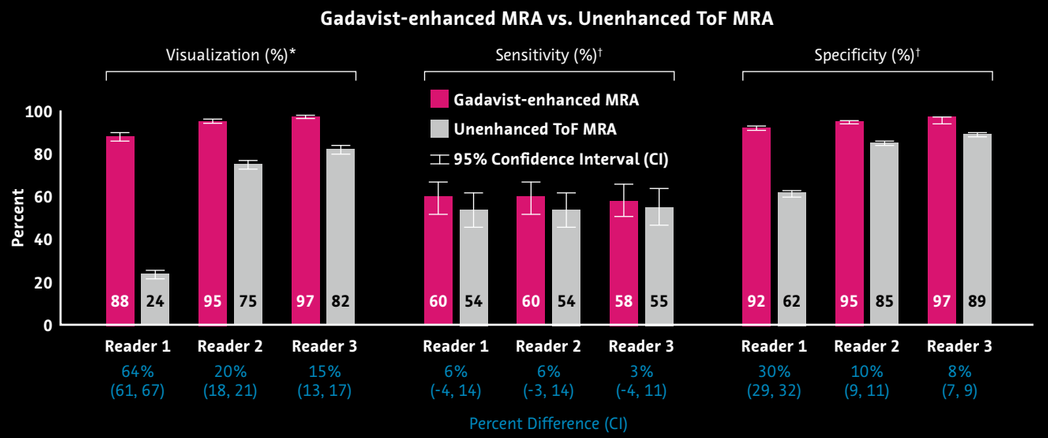
Gadavist-enhanced MRA



Findings: The ToF MRA demonstrates a long segment of signal loss in the region of interest, which was attributed to artifact by a majority of readers, particularly given the numerous additional areas of signal loss on the image. Gadavist-enhanced MRA, however, demonstrates a focal stenosis at the bifurcation, which is confirmed by Standard of Reference (SoR) CTA.

In a phase III clinical trial, Gadavist demonstrated superiority in visualization of supra-aortic arterial segments, and non-inferiority for sensitivity and specificity for clinically significant disease compared to unenhanced ToF MRA[1]

Study C: Diagnostic Performance of Gadavist-enhanced MRA[1]



* Superior vs. unenhanced ToF MRA † Non-inferior vs. unenhanced ToF MRA

Important Safety Information (continued)

Low Sensitivity for Significant Arterial Stenosis: The performance of Gadavist® MRA for detecting arterial segments with significant stenosis (>50% renal, >70% supra-aortic) has not been shown to exceed 55%. Therefore, a negative MRA study alone should not be used to rule out significant stenosis.

Please see additional Important Safety Information throughout this piece.

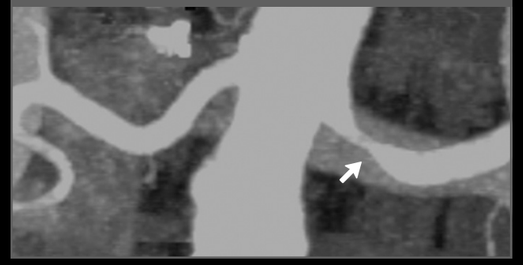
Compared to Unenhanced Magnetic Resonance Angiography (MRA):

See More With Gadavist

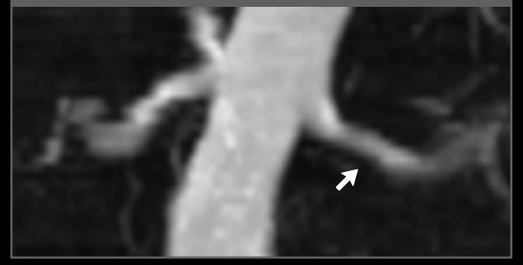
Case: Renal Magnetic Resonance Angiography

Patient History: 63-year-old male with a history of mild hypertension, smoking, diabetes, and aortic dissection.

Computed Tomography Angiography (CTA)



Unenhanced 2D Time-of-Flight (ToF) MRA



Gadavist MRA Parameters

Parameter	Value
Plane	Coronal
Mode	3D
Pulse sequence (SPGR, T1FFE, FLASH, etc.)	Incoherent gradient echo (spoiled)
Timing	Fluoro triggered/ bolus tracking method
TE	2 ms
TR	4 ms
Flip angle	20–40 (25 preferred)
NEX	1.0
Matrix (frequency × phase)	320 × 192
Slice thickness	2.25 mm
Spacing	Overlap 1 suggested
Voxel size (coronal)	1.25 × 1.75 × 2.0 mm
k-space	Elliptical centric filling
Acceleration factor (iPAT, ASSET, SENSE, GRAPPA, etc.)	2–4

Important Safety Information (continued)

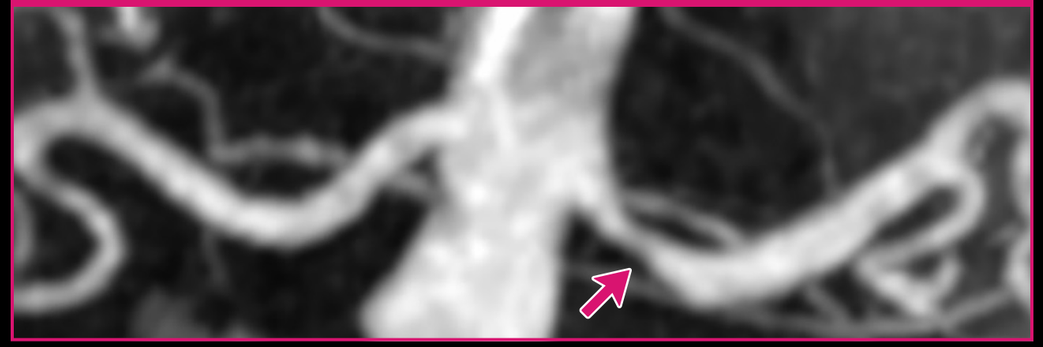
Acute Kidney Injury: In patients with chronic renal impairment, acute kidney injury sometimes requiring dialysis has been observed with the use of some GBCAs. Do not exceed the recommended dose; the risk of acute kidney injury may increase with higher than recommended doses.

Low Sensitivity for Significant Arterial Stenosis: The performance of Gadavist® MRA for detecting arterial segments with significant stenosis (>50% renal, >70% supra-aortic) has not been shown to exceed 55%. Therefore, a negative MRA study alone should not be used to rule out significant stenosis.

Please see additional Important Safety Information throughout this piece.

Case Source, Gadavist Phase III Clinical Trial

Gadavist-enhanced MRA

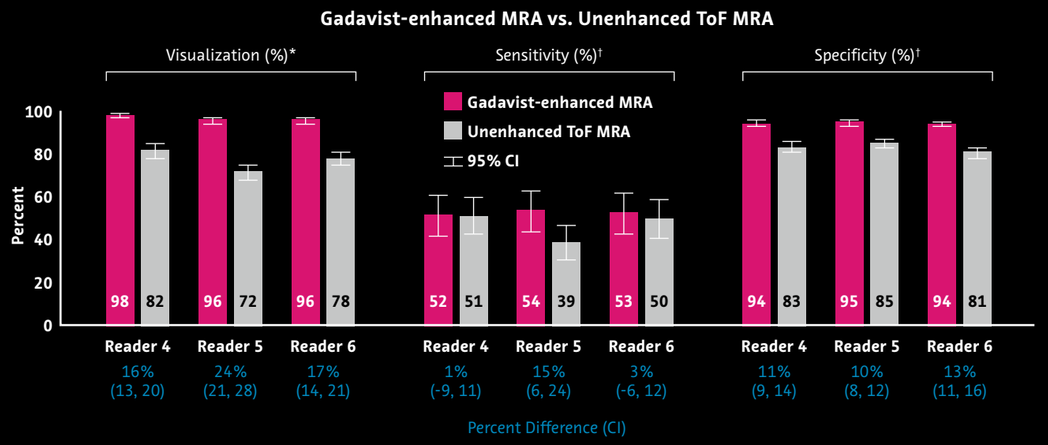


Findings: The ToF MRA does not demonstrate any stenosis of the left renal artery. Gadavist-enhanced MRA, however, demonstrates a moderate stenosis in the proximal left renal artery measuring 47%. This is confirmed by SoR CTA, which also demonstrates a moderate stenosis measuring 43%.

In a phase III clinical trial, compared to unenhanced ToF MRA, Gadavist demonstrated[1]:

- Superiority in visualization of renal arterial segments, and non-inferiority for sensitivity and specificity for clinically significant disease
- Identification of 10% more renal accessory arteries

Study D: Diagnostic Performance of Gadavist-enhanced MRA[1]



* Superior vs. unenhanced ToF MRA † Non-inferior vs. unenhanced ToF MRA

Cutting-edge Clinical Trials

Study C: 457 patients with known or suspected supra-aortic disease[1]

Study D: 292 patients with known or suspected renal artery disease[1]

COMPARATOR		SoR
MRA	MRA	
Unenhanced 2D Time-of-Flight	Gadavist-enhanced	CTA
Performed prior to Gadavist-enhanced MRA[1]	0.1 mmol/kg Gadavist administered via power injector[1]	Performed with minimum 64-slice scanner[2]

- Three central readers blinded to clinical information interpreted ToF and Gadavist-enhanced MRA images[1]
- Three additional blinded central readers interpreted separately acquired CTA images[1]

Primary Endpoints[1]

The efficacy of Gadavist-enhanced MRA was evaluated based on anatomical visualization and performance for evaluation of clinically significant disease.

- Visualization was defined as readers' ability to visualize each segment along its entire length
- Performance metrics included sensitivity and specificity of arterial segments with clinically significant stenosis, which was defined as at least 70% in Study C and 50% in Study D

Important Safety Information (continued)

Extravasation and Injection Site Reactions: Ensure catheter and venous patency before the injection of Gadavist®. Extravasation into tissues during Gadavist® administration may result in moderate irritation.

Overestimation of Extent of Malignant Disease in MRI of the Breast: Gadavist® MRI of the breast overestimated the histologically confirmed extent of malignancy in the diseased breast in up to 50% of the patients.

Please see additional Important Safety Information throughout this piece.

See the Difference

Gadavist: The first and only gadolinium-based contrast agent approved for MRA of the supra-aortic vasculature

Compared to Unenhanced ToF MRA, Gadavist-enhanced MRA Demonstrated[1]:

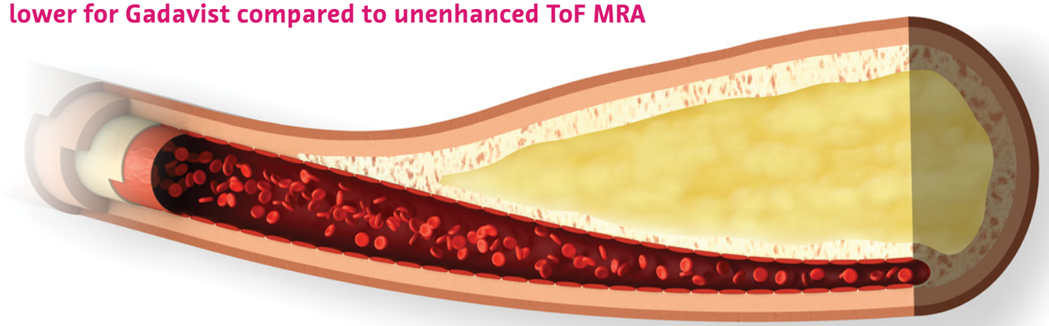
Visualization of more segments in supra-aortic and renal studies

Non-inferior sensitivity and specificity for clinically significant stenosis

	Visualization (%)		Sensitivity (%)		Specificity (%)	
	Study C	Study D	Study C	Study D	Study C	Study D
Gadavist-enhanced	**88–97%**	**96–98%**	**58–60%**	**52–54%**	**92–97%**	**94–95%**
Unenhanced	24–82%	72–82%	54–55%	39–51%	62–89%	81–85%
	13–61%	13–21%	-4 to -3%	-9 to 6%	7–29%	8–11%
	Lower bound of the 95% CI for the difference between Gadavist-enhanced and ToF MRA					

Improved visualization of accessory renal arteries for surgical planning and renal donor evaluation (Study D only). Of 1,752 main arteries visualized by the central CTA readers, 266 (15%) were also associated with positive visualization of at least one accessory (duplicate) artery. With the central MRA readers, the comparable rates were 232 of 1,752 (13%) for Gadavist MRA compared to 53 of 1,752 (3%) for ToF MRA.[1]

Variability in the amount of stenosis measured by the readers was high for CTA and MRA, but numerically lower for Gadavist compared to unenhanced ToF MRA



Strong Signal

A High Relaxivity* Gadolinium-based Contrast Agent

- Signal enhancement is based on multiple factors, including relaxivity and concentration[1]
- Stronger signal enhancement may improve tissue visualization in contrast-enhanced images[1]

Relaxivities of GBCAs[1]

Product Name	Relaxivity (r_1) at 1.5 Tesla*
Gadavist (gadobutrol)	**5.2**
MultiHance® (gadobenate)	6.3
Omniscan™ (gadodiamide)	4.3
Magnevist® (gadopentetate)	4.1
ProHance® (gadoteridol)	4.1
Optimark™ (gadoversetamide)	4.7
Dotarem® (gadoterate)	3.6

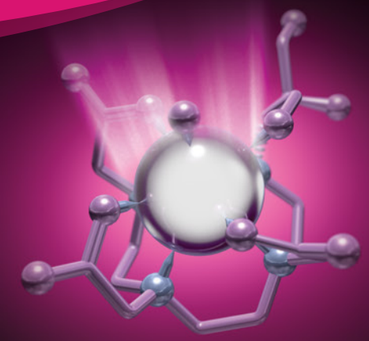
* Relaxivity of Gadavist is 5.2 $L \cdot mmol^{-1} \cdot s^{-1}$ at 1.5 Tesla (r_1 in plasma at 37°C)

Important Safety Information (continued)

Adverse Reactions: The most frequent (≥0.5%) adverse reactions associated with Gadavist® in clinical studies were headache (1.5%), nausea (1.1%) and dizziness (0.5%).

Please see additional Important Safety Information throughout this piece.

Strong Bond

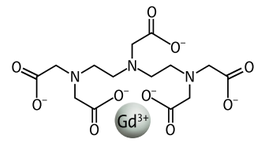


A Macrocyclic Gadolinium-based Contrast Agent

- There are two structural classes of Gd-chelate complexes: macrocyclic and linear[3]
- Macrocyclic structure imparts added strength compared with a linear structure[4]
- At pH 5.3 and 25°C, the dissociation half-life of Gadavist is 65 years, and at pH 7.4 the dissociation half-life is estimated to be >1,000 years[3,5]

Linear: Chain
Ligand chain wraps around Gd^{3+} ion[4]

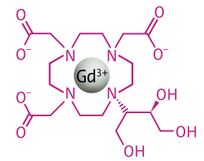
Magnevist® (gadopentetate)



Other Linear Agents Approved in the U.S.:[4]
MultiHance® (gadobenate), Omniscan™ (gadodiamide), Optimark™ (gadoversetamide)

Macrocyclic: Cage
Gd^{3+} caged in a rigid cavity of the ligand[4]

Gadavist® (gadobutrol)



Other Macrocyclic Agents Approved in the U.S.:[4]
Dotarem® (gadoterate), ProHance® (gadoteridol)

Important Safety Information

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

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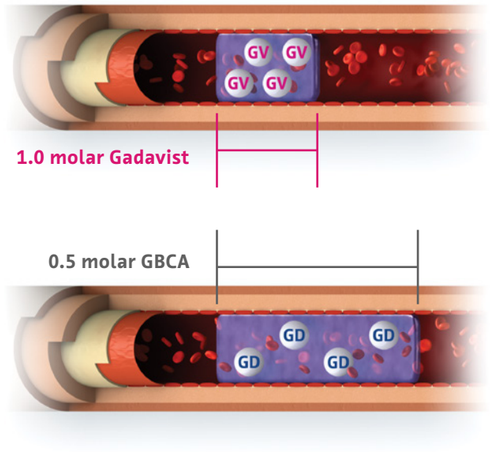
- The risk of NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or
  - Acute kidney injury
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended GADAVIST dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

Please see additional Important Safety Information throughout this piece.

High Concentration, Sufficient Acquisition Window

Double the Concentration, Half the Volume

- The recommended dose of Gadavist for adult and pediatric patients (including term neonates) is 0.1 mL/kg body weight (0.1 mmol/kg)[1]
- In MRA of adults, Gadavist should be administered by power injector at a flow rate of approximately 1.5 mL/second to extend the injection duration[1]
- For pediatric patients in MRA, administer Gadavist by power injector or manually, followed by a normal saline flush to ensure complete administration of the contrast (see section 2.2 in the Gadavist Package Insert)[1]
- Use bolus tracking technique to trigger the image acquisition following Gadavist administration[1]
- Follow Gadavist injection for MRA with a 30 cc saline flush to ensure complete administration of the contrast[1]



Important Safety Information (continued)

Contraindication and Important Information about Hypersensitivity Reactions: Gadavist® is contraindicated in patients with history of severe hypersensitivity reactions to Gadavist®. Anaphylactic and other hypersensitivity reactions with cardiovascular, respiratory, or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred following Gadavist® administration. Before Gadavist® administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Gadavist®.

Please see additional Important Safety Information throughout this piece.

Safety in Clinical Trials

Safety Profile Established in Clinical Trials of 6,809 Patients Worldwide[1]

Adverse reactions associated with the use of Gadavist are usually mild to moderate in severity and transient in nature. The adverse reactions that occurred in ≥0.1% subjects who received Gadavist were:

Reaction	Rate (%), n=6,809
Headache	1.5
Nausea	1.1
Dizziness	0.5
Dysgeusia	0.4
Feeling hot	0.4
Injection site reactions	0.4
Vomiting	0.4
Rash (includes generalized, macular, papular, pruritic)	0.3
Pruritus (includes generalized)	0.2
Erythema	0.2
Hypersensitivity/Anaphylactoid*	0.1
Dyspnea	0.1
Paresthesia	0.1

* Hypersensitivity/anaphylactoid reaction may occur with one or more of the following adverse reactions: for example, hypotension, urticaria, face edema, eyelid edema, flushing

Important Safety Information (continued)

Acute Kidney Injury: In patients with chronic renal impairment, acute kidney injury sometimes requiring dialysis has been observed with the use of some GBCAs. Do not exceed the recommended dose; the risk of acute kidney injury may increase with higher than recommended doses.

Please see additional Important Safety Information throughout this piece.

References: 1. Gadavist [package insert]. Whippany, NJ. Bayer HealthCare Pharmaceuticals Inc; 2011. **2.** Data on File. Bayer HealthCare Pharmaceuticals. **3.** Frenzel T, Lengsfeld P, Schirmer H, et al. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Invest Radiol.* 2008;43(12):817-828. **4.** Morcos SK. Extracellular gadolinium contrast agents: differences in stability. *Eur J Radiol.* 2008;66(2):175-179. **5.** Schmitt-Willich H. Stability of linear and macrocyclic gadolinium based contrast agents. *Br J Radiol.* 2007;80(955):581-583.

Bayer MR Portfolio Solutions

Bayer in Radiology leads with investment in development—from our roots in Medrad® injectors and contrast research, to state of the art equipment service and radiology informatics

Gadavist®
(gadobutrol) injection
1 mmol/mL

The High Relaxivity* 1.0 Molar Macrocyclic

MEDRAD® MRXperion™
MR Injection System

The MR SMART Injection System

Radimetrics™
Enterprise Platform

Seamlessly Smart

VirtualCare®
Remote Support

Remote Service Technology
Enables Advanced Diagnostics
and Real-time Support

Please see additional Important Safety Information for Gadavist throughout this piece.

See radiologysolutions.bayer.com for information about these and additional products.

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* Relaxivity of Gadavist is 5.2 $L \cdot mmol^{-1} \cdot s^{-1}$ at 1.5 Tesla (r_1 in plasma at 37°C)

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