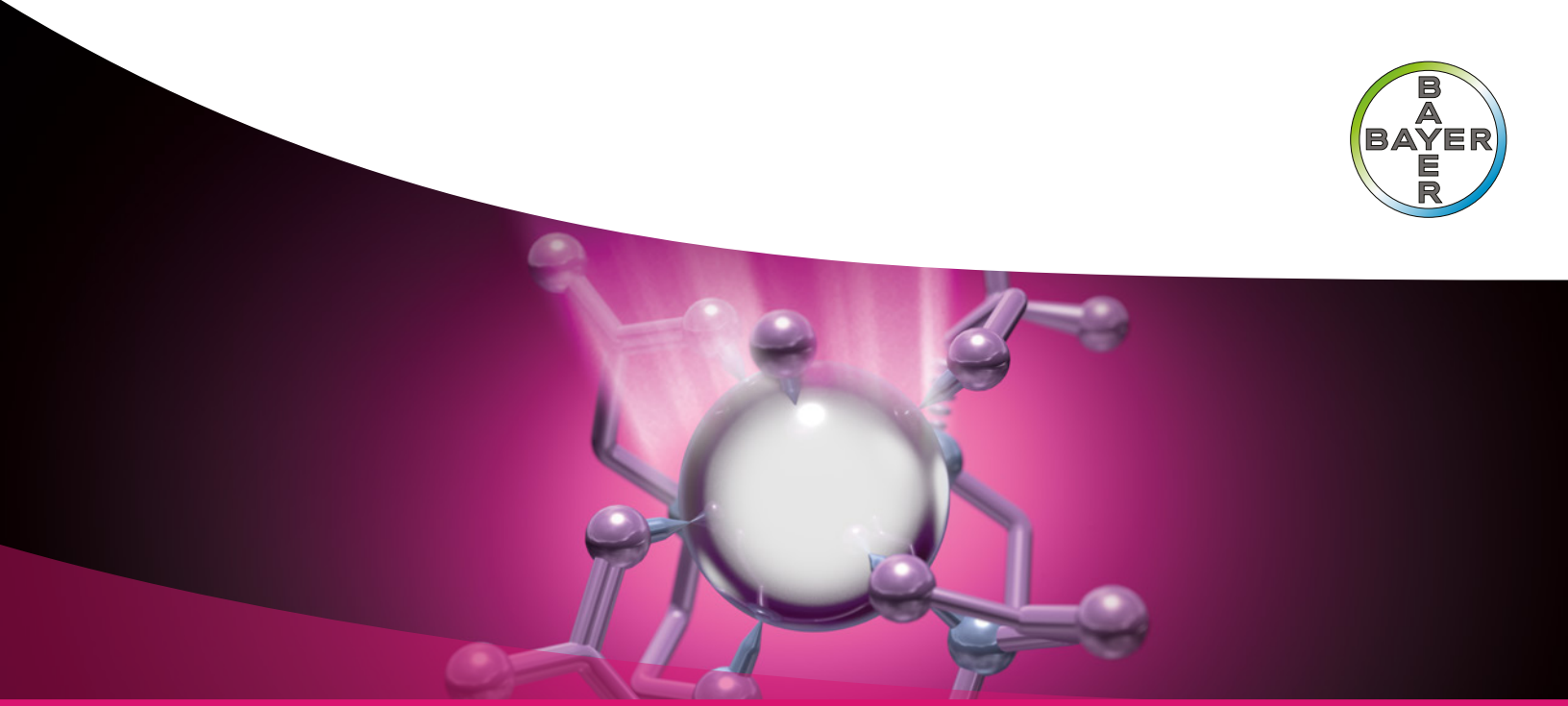


High Relaxivity.* Macrocyclic Bond.

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).

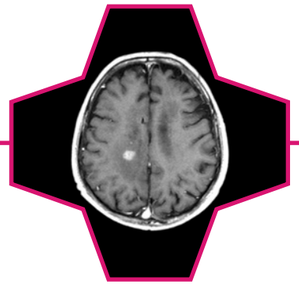
Learn more about Gadavist at gadavist.com

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

Gadavist®
(gadobutrol) injection
1 mmol/mL

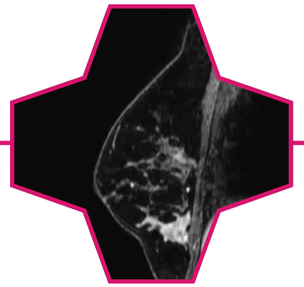
Indications Matter

Is your MRI contrast agent approved for these indications?



March 2011

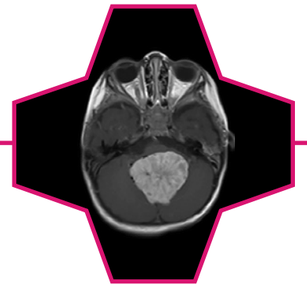
Gadavist approved for central nervous system (CNS) MRI in adults and pediatric patients 2 years of age and older



June 2014

Additional approval for MRI of the breast to assess the presence and extent of malignant breast disease

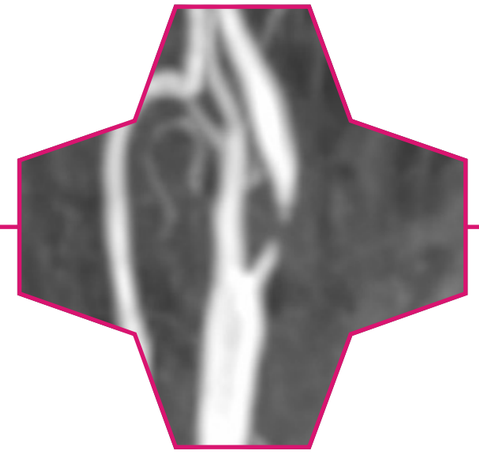
First and only GBCA
indicated for breast MRI



December 2014

CNS MRI indication expanded to include pediatric patients less than 2 years of age

First and only GBCA
indicated for MRI of the CNS in patients less than 2 years of age (including term neonates)



April 2016

Gadavist approved for MRA to evaluate known or suspected supra-aortic or renal artery disease in adult and pediatric patients (including term neonates)

First and only GBCA
indicated for MRA of the supra-aortic vasculature

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®.

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.

Images courtesy of Gadavist U.S. Phase III Clinical Trials, Gillian Newstead, MD, FACR, and Ravi Bhargava, MD, FRCPC, Stollery Children's Hospital, University of Alberta, Edmonton, Alberta, Canada.

Important Safety Information (continued)

Pediatric Use: The safety and effectiveness of Gadavist® have been established in pediatric patients born at 37 weeks gestation or later based on imaging and pharmacokinetic data in 135 patients ages 2 to 17 years and 44 patients ages 0 to less than 2 years and extrapolation from adult data. No dose adjustment according to age is necessary in pediatric patients. The safety and effectiveness of Gadavist® have not been established in premature infants.

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.

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)

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.

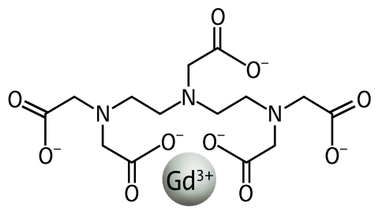
Strong Bond

A Macrocyclic Gadolinium-based Contrast Agent

- There are two structural classes of Gd-chelate complexes: macrocyclic and linear[2]
- Macrocyclic structure imparts added strength compared with a linear structure[3]
- 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[2,4]

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

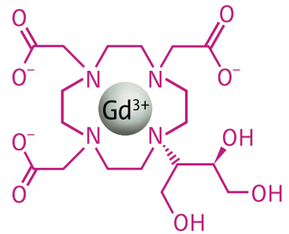
Magnevist® (gadopentetate)



Other Linear Agents Approved in the U.S.:[3]
MultiHance® (gadobenate), Omniscan™ (gadodiamide), Optimark™ (gadoversetamide)

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

Gadavist® (gadobutrol)



Other Macrocyclic Agents Approved in the U.S.:[3]
Dotarem® (gadoterate), ProHance® (gadoteridol)

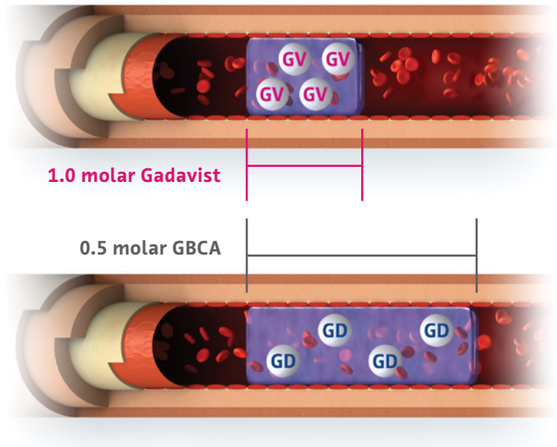
Important Safety Information (continued)

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.

Please see additional Important Safety Information throughout this piece.

Double the Concentration, Half the Volume

For Adults and Pediatric Patients (Including Term Neonates), the Recommended Dose of Gadavist Is 0.1 ml/kg Body Weight (0.1 mmol/kg)



Due to its 1.0 molar concentration, Gadavist is approved at a dose that is half the volume of 0.5 molar gadolinium-based contrast agents (GBCAs), with a more compact bolus.[1]

Body Weight		Total Volume (mL)
lb	kg	1 Molar Gadavist
5.5	2.5	0.25
11	5	0.5
22	10	1
33	15	1.5
44	20	2
55	25	2.5
66	30	3
77	35	3.5
88	40	4
99	45	4.5
110	50	5
132	60	6
154	70	7
176	80	8
198	90	9
220	100	10
242	110	11
264	120	12
286	130	13
308	140	14

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.

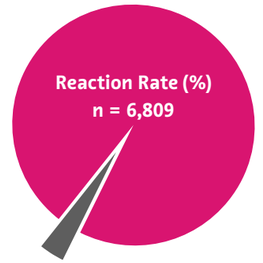
Safety in Clinical Trials

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

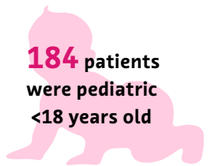
Adverse reactions associated with the use of Gadavist are usually mild to moderate in severity and transient in nature. The adverse reactions that occurred in ≥0.1% subjects who received Gadavist were:

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



4% of patients experienced one or more adverse reactions[1]



184 patients were pediatric <18 years old

Important Safety Information (continued)

Pediatric Use: The safety and effectiveness of Gadavist® have been established in pediatric patients born at 37 weeks gestation or later based on imaging and pharmacokinetic data in 135 patients ages 2 to 17 years and 44 patients ages 0 to less than 2 years and extrapolation from adult data. No dose adjustment according to age is necessary in pediatric patients. The safety and effectiveness of Gadavist® have not been established in premature infants.

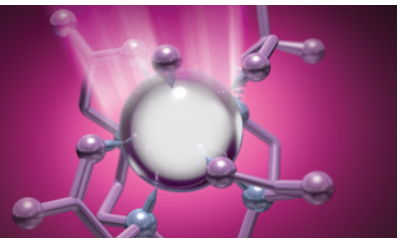
Please see additional Important Safety Information throughout this piece.

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

High Relaxivity.* Macrocyclic Bond.



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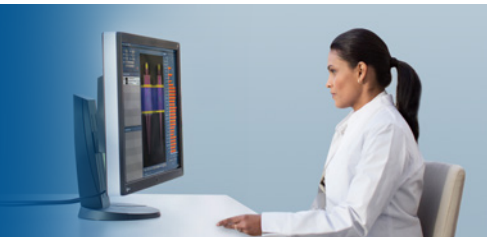

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Please see additional Important Safety Information for Gadavist throughout this piece.

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)

References: 1. Gadavist [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2011. **2.** 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. **3.** Morcos SK. Extracellular gadolinium contrast agents: differences in stability. *Eur J Radiol.* 2008;66(2):175-179. **4.** Schmitt-Willich H. Stability of linear and macrocyclic gadolinium based contrast agents. *Br J Radiol.* 2007;80(955):581-583.

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