HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Gadavist safely and effectively. See full prescribing information for Gadavist.

Gadavist (gadobutrol) injection, for intravenous use
Initial U.S. Approval: 2011

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
See full prescribing information for complete boxed warning

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.

- **The risk for 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 (5.1).**

----------INDICATIONS AND USAGE----------

Gadavist is a gadolinium-based contrast agent indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system. (1)

----------DOSAGE AND ADMINISTRATION----------

Gadavist is formulated at a higher concentration (1 mmol/mL) compared to certain other gadolinium-based contrast agents, resulting in a lower volume of administration. Use the table in section 2.1 to determine the volume of Gadavist to be administered.

The recommended dose of Gadavist is 0.1 mL/kg body weight (0.1 mmol/kg), administered as an intravenous bolus injection at a flow rate of approximately 2 mL/second. Flush the intravenous cannula with physiological saline solution after the injection. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Gadavist injection contains 1 mmol gadobutrol/mL (equivalent to 604.72 mg gadobutrol/mL) and is available in vials and prefilled syringes (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeated dosing appears to increase the risk. (5.1)
- Hypersensitivity: Anaphylactoid/anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred. Monitor patients closely for need of emergency cardiorespiratory support. (5.2)

----------ADVERSE REACTIONS----------

- The most frequent (≥ 0.5%) adverse reactions associated with Gadavist in clinical studies were headache, nausea, injection site reaction, dysgeusia and feeling hot. (6.1)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING 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 for 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 *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Gadavist is a gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.

2 DOSAGE AND ADMINISTRATION

Gadavist is formulated at a higher concentration (1 mmol/mL) compared to certain other gadolinium based contrast agents, resulting in a lower volume of administration. Closely examine the table below to determine the volume to be administered.

2.1 Adults and Children (2 years and older)

The recommended dose of Gadavist is 0.1 mL/kg body weight (0.1 mmol/kg).

VOLUME OF GADAVIST INJECTION BY BODY WEIGHT		
BODY WEIGHT		Volume to be administered, mL
lb	kg	
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
298	140	14

- Visually inspect Gadavist for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored, if particulate matter is present or if the container appears damaged.
- Administer Gadavist as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second. Flush the intravenous cannula with physiological saline solution after the injection.

2.2 Dosing Guidelines

- Sterile technique must always be used when preparing and administering injection of contrast media. Do not mix Gadavist with other drugs.
- Contrast-enhanced MRI can commence immediately following contrast administration.

Vials

- Draw Gadavist into the syringe immediately before use.
- Do not pierce the rubber stopper more than once. Discard any unused vial contents.

Pre-filled syringes

- Remove the tip cap from the pre-filled syringe immediately before use. Discard any unused syringe contents.

3 DOSAGE FORMS AND STRENGTHS

Gadavist is a sterile, clear, colorless to pale yellow solution for injection containing 1 mmol gadobutrol per milliliter (equivalent to 604.72 mg gadobutrol/mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30–59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60–89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following Gadavist administration to Bayer Healthcare (1-888-842-2937) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (for example, age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. 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 prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's

elimination. The usefulness of hemodialysis in the prevention of NSF is unknown *[see Clinical Pharmacology (12) and Dosage and Administration (2)]*.

5.2 Hypersensitivity Reactions

Anaphylactoid and anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred following Gadavist administration *[see Adverse Reactions (6)]*.

- 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.
- Administer Gadavist only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.

Most hypersensitivity reactions to Gadavist have occurred within half an hour after administration. Delayed reactions can occur up to several days after administration. Observe patients for signs and symptoms of hypersensitivity reactions during and following Gadavist administration.

5.3 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. Avoid intramuscular administration of Gadavist *[see Nonclinical Toxicology (13.2)]*.

6 ADVERSE REACTIONS

The most serious reactions to Gadavist are nephrogenic systemic fibrosis and hypersensitivity reactions *[see Warnings and Precautions (5.1 and 5.2)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect Gadavist exposure in 4549 subjects (4411 adults and 138 children aged 2–17) who received a dose that ranged from <0.09 to 0.51 mmol/kg body weight; the majority (n=2434) received the recommended dose of 0.1 (±0.01) mmol/kg body weight. Overall, 58.5% of the subjects were men and the ethnic distribution was 64.8% Caucasian, 27.3% Asian, 3% Hispanic, 1.3% Black, and 3.6% patients of other ethnic groups. The average age was 54.2 years (range from 2 to 93 years).

Overall, 4% of subjects reported one or more adverse reactions during a follow-up period that ranged from 24 hours to 7 days after Gadavist administration.

Adverse reactions associated with the use of Gadavist are usually mild to moderate in severity and transient in nature.

Table 1 lists adverse reactions that occurred in ≥0.1% subjects who received Gadavist.

Table 1: Adverse Reactions

Reaction	Rate (%) n=4549
Headache	1.5
Nausea	1.2
Injection site reactions	0.6
Dysgeusia	0.5
Feeling Hot	0.5
Dizziness	0.4
Vomiting	0.4
Rash (includes generalized, macular, papular, pruritic)	0.3
Pruritus (includes generalized)	0.2
Erythema	0.2
Dyspnea	0.2
Paresthesia	0.1

Adverse reactions that occurred with a frequency of <0.1% in subjects who received Gadavist include: hypersensitivity/anaphylactoid reactions (hypotension, urticaria, flushing, pallor), loss of consciousness, convulsion, parosmia, tachycardia, palpitation, dry mouth, malaise and feeling cold.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported during postmarketing use of Gadavist. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cardiac arrest
- Nephrogenic Systemic Fibrosis (NSF)
- Hypersensitivity/anaphylactoid reactions (anaphylactoid shock, circulatory collapse, blood pressure increased, chest pain, respiratory arrest, bronchospasm, cyanosis, oropharyngeal swelling, laryngeal edema, face edema, angioedema, conjunctivitis, eyelid edema, hyperhidrosis, cough, sneezing, and burning sensation) *[see Warnings and Precautions (5.2)]*

7 DRUG INTERACTIONS

There are no known drug interactions. Gadavist does not interfere with serum and plasma calcium measurements determined by colorimetric assays. Do not mix Gadavist with other drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Gadavist in pregnant women. While it is unknown if Gadavist crosses the human placenta, other gadolinium-based contrast agents (GBCAs) do cross the placenta in humans and result in fetal exposure. Limited published human data on exposure to other GBCAs during pregnancy did not show adverse effects in exposed neonates. Gadavist should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retardation of the embryonal development and embryolethality occurred in pregnant rats receiving maternally toxic doses of Gadavist (≥7.5 mmol/kg body weight) that were 12 times the human equivalent dose based on body surface area and in pregnant rabbits receiving doses (≥2.5 mmol/kg body weight) that were 8 times the recommended human dose (based on body surface area). In rabbits, this finding occurred without evidence of pronounced maternal toxicity and with minimal placental transfer (0.01% of the administered dose detected in the fetuses).

Gadavist was not teratogenic when given intravenously to monkeys during organogenesis at doses up to 8 times the recommended single human dose (based on body surface area) but was embryolethal at that dose. Because pregnant animals received repeated daily doses of Gadavist, their overall exposure was significantly higher than that achieved with the standard single dose administered to humans.

8.3 Nursing Mothers

It is not known whether gadobutrol is excreted in human milk. Limited case reports on use of GBCAs in nursing mothers indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in human breast milk. Studies have shown limited GBCA gastrointestinal absorption. Nonclinical data show that gadobutrol is excreted into breast milk in very small amounts (<0.1% of the dose intravenously administered) and the absorption via the gastrointestinal tract is poor (approximately 5% of the dose orally administered was excreted in the urine) *[see Clinical Pharmacology (12.3)]*. In lactating rats given 0.5 mmol/kg of intravenous [^{153}Gd]-gadobutrol, 0.01% of the total administered radioactivity was transferred to the neonate via maternal milk, mostly within 3 hours after the intravenous administration. Because many drugs are excreted in human milk, exercise caution when gadobutrol is administered to a nursing woman.

8.4 Pediatric Use

The pharmacokinetics, safety and efficacy of Gadavist at a single dose of 0.1 mmol/kg have been established in children 2 to 17 years of age. No dose adjustment according to age is necessary in this population. The safety and effectiveness of Gadavist have not been established in children below two years of age. *[See Dosage and Administration (2.1), Clinical Pharmacology (12.3).]*

8.5 Geriatric Use

In clinical studies of Gadavist, 1377 patients were 65 years of age and over, while 104 patients were 80 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, use of Gadavist in elderly patients should be cautious, reflecting the greater frequency of impaired renal function and concomitant disease or other drug therapy. No dose adjustment according to age is necessary in this population.

8.6 Renal Impairment

Prior to administration of Gadavist, screen all patients for renal dysfunction by obtaining a history and/or laboratory tests *[see Warnings and Precautions (5.1)]*. No dosage adjustment is recommended for patients with renal impairment.

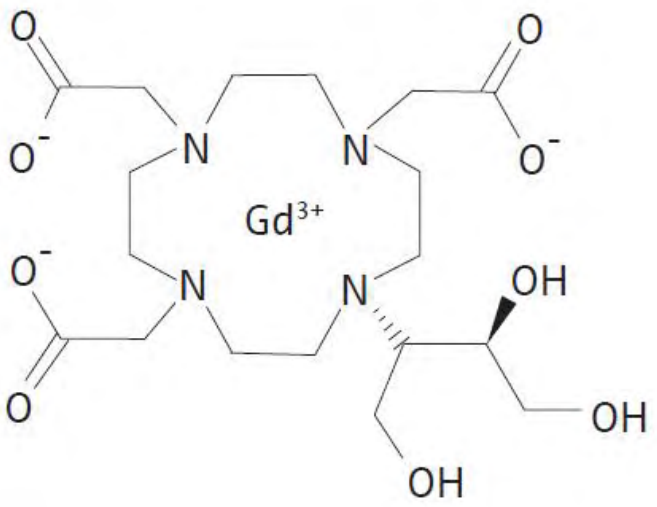
Gadavist can be removed from the body by hemodialysis *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The maximum dose of Gadavist tested in healthy volunteers, 1.5 mL/kg body weight (1.5 mmol/kg) (15 times the recommended dose), was tolerated in a manner similar to lower doses. Gadavist can be removed by hemodialysis *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Gadavist (gadobutrol) Injection is a paramagnetic macrocyclic contrast agent administered for magnetic resonance imaging. The chemical name for gadobutrol is 10–[(1SR,2RS)–2,3–dihydroxy–1–hydroxymethylpropyl]–1,4,7,10–tetraazacyclododecane–1,4,7–triacetic acid, gadolinium complex. Gadobutrol has a molecular formula of $C_{18}H_{31}GdN_4O_9$ and a molecular weight of 604.72.



Gadavist is a clear, colorless to pale yellow solution containing 1 mmol gadobutrol (equivalent to 604.72 mg gadobutrol) per mL as the active ingredient and the excipients calcobutrol sodium, trometamol, hydrochloric acid (for pH adjustment) and water for injection. Gadavist contains no preservatives.

The main physico-chemical properties of Gadavist (1 mmol/mL solution for injection) are listed below:

Osmolarity at 37°C (mOsm/L solution)	1117
Osmolality at 37°C (mOsm/kg H_2O)	1603
Viscosity at 37°C (mPa·s)	4.96
pH	6.6–8

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with:

- Differences in proton density
- Differences of the spin-lattice or longitudinal relaxation times (T_1)
- Differences in the spin-spin or transverse relaxation time (T_2)

When placed in a magnetic field, Gadavist shortens the T_1 and T_2 relaxation times. The extent of decrease of T_1 and T_2 relaxation times, and therefore the amount of signal enhancement obtained from Gadavist, is based upon several factors including the concentration of Gadavist in the tissue, the field strength of the MRI system, and the relative ratio of the longitudinal and transverse relaxation times. At the recommended dose, the T_1 shortening effect is observed with greatest sensitivity in T_1-weighted magnetic resonance sequences. In T2*-weighted sequences the induction of local magnetic field inhomogeneities by the large magnetic moment of gadolinium and at high concentrations (during bolus injection) leads to a signal decrease.

12.2 Pharmacodynamics

Gadavist leads to distinct shortening of the relaxation times even in low concentrations. At pH 7, 37°C and 1.5 T, the relaxivity (r_1) - determined from the influence on the relaxation times (T_1) of protons in plasma - is 5.2 L/(mmol·sec) and the relaxivity (r_2) - determined from the influence on the relaxation times (T_2) - is 6.1 L/(mmol·sec). These relaxivities display only slight dependence on the strength of the magnetic field. The T_1 shortening effect of paramagnetic contrast agents is dependent on concentration and r_1 relaxivity (see Table 2). This may improve tissue visualization.

Table 2: Relaxivity (r_1) of Gadolinium Chelates at 1.5 T

Gadolinium-Chelate	r_1 ($L \cdot mmol^{-1} \cdot s^{-1}$)
Gadobutrol	5.2
Gadoteridol	4.1
Gadobenate	6.3
Gadopentetate	4.1
Gadodiamide	4.3
Gadoversetamide	4.7

r_1 relaxivity in plasma at 37°C

Compared to 0.5 molar gadolinium-based contrast agents, the higher concentration of Gadavist results in half the volume of administration and a more compact contrast bolus.

Gadavist is a highly water-soluble, extremely hydrophilic compound with a partition coefficient between n-butanol and buffer at pH 7.6 of about 0.006.

12.3 Pharmacokinetics

Distribution

After intravenous administration, gadobutrol is rapidly distributed in the extracellular space. After a gadobutrol dose of 0.1 mmol/kg body weight, an average level of 0.59 mmol gadobutrol/L was measured in plasma 2 minutes after the injection and 0.3 mmol gadobutrol/L 60 minutes after the injection. Gadobutrol does not display any particular protein binding. In rats, gadobutrol does not penetrate the intact blood-brain barrier.

Metabolism

Gadobutrol is not metabolized.

Elimination

Gadobutrol is excreted in an unchanged form via the kidneys. Gadobutrol is eliminated from plasma with a mean terminal half-life of 1.81 hours (1.33–2.13 hours).

In healthy subjects, renal clearance of gadobutrol is 1.1 to 1.7 mL/(min·kg) and thus comparable to the renal clearance of inulin, confirming that gadobutrol is eliminated by glomerular filtration.

Within two hours after intravenous administration more than 50% and within 12 hours more than 90% of the given dose is eliminated via the urine. The extrarenal elimination is negligible.

Special populations

Gender

Gender has no clinically relevant effect on the pharmacokinetics of gadobutrol.

Geriatric

A single IV dose of 0.1 mmol/kg Gadavist was administered to 15 elderly and 16 non-elderly subjects. AUC was slightly higher and clearance slightly lower in elderly subjects as compared to non-elderly subjects *[see Use in Specific Populations (8.5)]*.

Pediatric

The pharmacokinetics of Gadavist were evaluated based on a population pharmacokinetic analysis in 130 pediatric subjects aged 2 to 17 years. Subjects received a single intravenous dose of 0.1 mmol/kg of Gadavist. The median AUC (mmol·h/L), clearance (L/hr/kg) and elimination half-life (hrs) of gadobutrol was similar across the age range of 2 – 17 years. The median AUC of gadobutrol in children 2 – 6 years (n=45) was 0.8 mmol·h/L, 1.0 mmol·h/L in children 7 – 11 years (n=39), and 1.2 mmol·h/L in children 12 – 17 years (n=46). The median clearance of gadobutrol in children 2 – 6 years was 0.13 L/hr/kg, 0.1 L/hr/kg in children 7 – 11 years, and 0.09 L/hr/kg in children 12 – 17 years, and the median elimination half-life of gadobutrol in children 2 – 6 years was 1.75 hours, 1.61 hours in children 7 – 11 years, and 1.65

hours in children 12 – 17 years. Approximately 99% (median value) of the dose was recovered in urine within 6 hours. *[See Use in Specific Populations (8.4).]*

Renal Impairment

In patients with impaired renal function, the serum half-life of gadobutrol is prolonged and correlated with the reduction in creatinine clearance.

After intravenous injection of 0.1 mmol gadobutrol/kg body weight, the elimination half-life was 5.8 ± 2.4 hours in mild to moderately impaired patients ($80>CL_{CR}>30$ mL/min) and 17.6 ± 6.2 hours in severely impaired patients not on dialysis ($CL_{CR} < 30$ mL/min). The mean AUC of gadobutrol in patients with normal renal function was 1.1 ± 0.1 mmol·h/L, compared to 4.0 ± 1.8 mmol·h/L in patients with mild to moderate renal impairment and 11.5 ± 4.3 mmol·h/L in patients with severe renal impairment.

Complete recovery in the urine was seen in patients with mild or moderate renal impairment within 72 hours. In patients with severely impaired renal function at least 80% of the administered dose was recovered in the urine within 5 days.

For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of Gadavist in order to enhance the contrast agent's elimination. Sixty-eight % of gadobutrol is removed from the body after the first dialysis, 94% after the second dialysis, and 98% after the third dialysis session. *[See Warnings and Precautions (5.1) and Use in Specific Populations (8.6).]*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies of gadobutrol have been conducted.

Gadobutrol was not mutagenic in *in vitro* reverse mutation tests in bacteria, in the HGPRT (hypoxanthine-guanine phosphoribosyl transferase) test using cultured Chinese hamster V79 cells, or in chromosome aberration tests in human peripheral blood lymphocytes, and was negative in an *in vivo* micronucleus test in mice after intravenous injection of 0.5 mmol/kg.

Gadobutrol had no effect on fertility and general reproductive performance of male and female rats when given in doses 12.2 times the human equivalent dose (based on body surface area).

13.2 Animal Toxicology and/or Pharmacology

Local intolerance reactions, including moderate irritation associated with infiltration of inflammatory cells was observed after paravenous administration to rabbits, suggesting the possibility of occurrence of local irritation if the contrast medium leaks around veins in a clinical setting *[see Warnings and Precautions (5.3)]*.

14 CLINICAL STUDIES

Patients referred for MRI of the central nervous system with contrast were enrolled in two clinical trials that evaluated the visualization characteristics of lesions. In both studies, patients underwent a baseline, pre-contrast MRI prior to administration of Gadavist at a dose of 0.1 mmol/kg, followed by a post-contrast MRI. In study A, patients also underwent an MRI before and after the administration of gadoteridol. The studies were designed to demonstrate superiority of Gadavist MRI to non-contrast MRI for lesion visualization. For both studies, pre-contrast and pre-plus-post contrast images (paired images) were independently evaluated by three readers for contrast enhancement and border delineation using a scale of 0 to 4, and for internal morphology using a scale of 0 to 3 (Table 3). Lesion counting was also performed to demonstrate non-inferiority of paired Gadavist image sets to pre-contrast MRI. Readers were blinded to clinical information.

Table 3: Primary Endpoint Visualization Scoring System

Score	Visualization Characteristics		
	Contrast Enhancement	**Border Delineation**	**Internal Morphology**
1	None	None	Poorly visible
2	Weak	Moderate	Moderately visible

3	Clear	Clear but incomplete	Sufficiently visible
4	Clear and bright	Clear and complete	N/A

Diagnostic efficacy was determined in 657 subjects. The average age was 49 years (range 18 to 85 years) and 42% were male. The ethnic representations were 39% Caucasian, 4% Black, 16% Hispanic, 38% Asian, and 3% of other ethnic groups.

Table 4 shows a comparison of visualization results between paired images and pre-contrast images. Gadavist provided a statistically significant improvement for each of the three lesion visualization parameters when averaged across three independent readers for each study.

Table 4: Visualization Endpoint Results of Central Nervous System Adult MRI Studies with 0.1 mmol/kg Gadavist

Endpoint	**Study A N=336**			**Study B N=321**		
	Pre-contrast	Paired	Difference*	Pre-contrast	Paired	Difference
Contrast Enhancement	0.97	2.26	1.29^	0.93	2.86	1.94^
Border Delineation	1.98	2.58	0.60^	1.92	2.94	1.02^
Internal Morphology	1.32	1.93	0.60^	1.57	2.35	0.78^
Average # Lesions Detected	8.08	8.25	0.17**	2.65	2.97	0.32^^

* Difference of means = (paired mean) – (pre-contrast mean)
^ $p<0.001$
^^ Met noninferiority margin of -0.35
** Did not meet noninferiority margin of -0.35

Performances of Gadavist and gadoteridol for visualization parameters were similar. Regarding the number of lesions detected, study B met the prespecified noninferiority margin of -0.35 for paired read versus pre-contrast read while in Study A, Gadavist and gadoteridol did not.

For the visualization endpoints contrast enhancement, border delineation, and internal morphology, the percentage of patients scoring higher for paired images compared to pre-contrast images ranged from 93% to 99% for Study A, and 95% to 97% for Study B. For both studies, the mean number of lesions detected on paired images exceeded that of the pre-contrast images; 37% for Study A and 24% for Study B. There were 29% and 11% of subjects in which the pre-contrast images detected more lesions for Study A and Study B, respectively.

The percentage of patients whose average reader mean score changed by ≤ 0, up to 1, up to 2, and ≥ 2 scoring categories presented in Table 3 is shown in Table 5. The categorical improvement of (≤ 0) represents higher (< 0) or identical ($= 0$) scores for the pre-contrast read, the categories with scores > 0 represent the magnitude of improvement seen for the paired read.

Table 5: Primary Endpoint Visualization Categorical Improvement for Average Reader

	Study A N=336				**Study B N=321**			
Endpoint	**Categorical Improvement (Paired – Pre-Contrast) %**				**Categorical Improvement (Paired – Pre-Contrast) %**			
	≤0	>0 – <1	1 – <2	≥2	≤0	>0 – <1	1 – <2	≥2
Contrast Enhancement	1	30	55	13	3	6	34	57
Border Delineation	7	73	18	1	5	38	51	5
Internal Morphology	4	79	17	0	5	61	33	1

For both studies, the improvement of visualization endpoints in paired Gadavist images compared to pre-contrast images resulted in improved assessment of normal and abnormal CNS anatomy.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gadavist is a clear, colorless to pale yellow solution containing 1 mmol gadobutrol per milliliter (equivalent to 604.72 mg gadobutrol) per mL. Gadavist is supplied in the following sizes:

Single-Dose Vials

7.5 mL single-dose vials, rubber stoppered in cartons of 10, Boxes of 20	(NDC 50419-325-11)
10 mL single-dose vials, rubber stoppered, in cartons of 10, Boxes of 20	(NDC 50419-325-12)
15 mL single-dose vials, rubber stoppered, in cartons of 10, Boxes of 20	(NDC 50419-325-13)

Single-Dose Pre-Filled Syringes

7.5 mL single-dose pre-filled disposable syringes, Boxes of 5	(NDC 50419-325-27)
10 mL single-dose pre-filled disposable syringes, Boxes of 5	(NDC 50419-325-28)
15 mL single-dose pre-filled disposable syringes, Boxes of 5	(NDC 50419-325-29)

16.2 Storage and Handling

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Should freezing occur, Gadavist should be brought to room temperature before use. If allowed to stand at room temperature, Gadavist should return to a clear, colorless to pale yellow solution. Visually inspect Gadavist for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored, if particulate matter is present or if the container appears damaged.

17 PATIENT COUNSELING INFORMATION

17.1 Nephrogenic Systemic Fibrosis

Instruct patients to inform their physician if they:

- Have a history of kidney disease and/or liver disease, or
- Have recently received a GBCA

GBCAs increase the risk of NSF among patients with impaired elimination of drugs. To counsel patients at risk of NSF:

- Describe the clinical manifestation of NSF
- Describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following Gadavist administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

17.2 Common Adverse Reactions

Inform patients that they may experience:

- Reactions along the venous injection site, such as mild and transient burning or pain or feeling of warmth or coldness at the injection site
- Side effects of headache, nausea, abnormal taste and feeling hot

17.3 General Precautions

Instruct patients receiving Gadavist to inform their physician if they:

- Are pregnant or breastfeeding
- Have a history of allergic reaction to contrast media, bronchial asthma or allergic respiratory disorder,

- Are taking any medications

Manufactured for:

Bayer HealthCare Pharmaceuticals

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Manufactured in Germany

US Patent No. 5,980,864 and 5,871,709
March 2011

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Gadavist safely and effectively. See full prescribing information for Gadavist.
Gadavist (gadobutrol) injection, for intravenous use
Initial U.S. Approval: 2011

PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
See full prescribing information for complete boxed warning

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.

- **The risk for 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 (5.1).**

----------INDICATIONS AND USAGE----------

Gadavist is a gadolinium-based contrast agent indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system. (1)

----------DOSAGE AND ADMINISTRATION----------

Gadavist is formulated at a higher concentration (1 mmol/mL) compared to certain other gadolinium-based contrast agents, resulting in a lower volume of administration. Use the table in section 2.1 to determine the volume of Gadavist to be administered.

The recommended dose of Gadavist is 0.1 mL/kg body weight (0.1 mmol/kg), administered as an intravenous bolus injection at a flow rate of approximately 2 mL/second. Flush the intravenous cannula with physiological saline solution after the injection. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Pharmacy Bulk Packages are not for use in direct intravenous infusions. (2)

Gadavist injection contains 1 mmol gadobutrol/mL (equivalent to 604.72 mg gadobutrol/mL). (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeated dosing appears to increase the risk. (5.1)
- Hypersensitivity: Anaphylactoid/anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred. Monitor patients closely for need of emergency cardiorespiratory support. (5.2)

----------ADVERSE REACTIONS----------

- The most frequent (≥ 0.5%) adverse reactions associated with Gadavist in clinical studies were headache, nausea, injection site reaction, dysgeusia and feeling hot. (6.1)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING 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 for 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 *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Gadavist is a gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.

2 DOSAGE AND ADMINISTRATION

Gadavist is formulated at a higher concentration (1 mmol/mL) compared to certain other gadolinium based contrast agents, resulting in a lower volume of administration. Closely examine the table below to determine the volume to be administered.

2.1 Adults and Children (2 years and older)

The recommended dose of Gadavist is 0.1 mL/kg body weight (0.1 mmol/kg).

VOLUME OF GADAVIST INJECTION BY BODY WEIGHT		
BODY WEIGHT		Volume to be administered, mL
lb	kg	
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
298	140	14

- Visually inspect Gadavist for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored, if particulate matter is present or if the container appears damaged.
- Administer Gadavist as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second. Flush the intravenous cannula with physiological saline solution after the injection.

2.2 Dosing Guidelines

- Sterile technique must always be used when preparing and administering injection of contrast media. Do not mix Gadavist with other drugs.
- Contrast-enhanced MRI can commence immediately following contrast administration.
- Instructions of the device manufacturer must be followed.

Pharmacy Bulk Package Preparation

- Pharmacy Bulk Packages are not for use in direct intravenous infusions.
- After the Pharmacy Bulk Package has been opened, Gadavist remains stable for 24 hours at 20–25°C (68–77°F).
- The Pharmacy Bulk Package is used as a multiple dose container with an appropriate transfer device for filling empty sterile syringes.
- The transfer of Gadavist from the Pharmacy Bulk Package must be performed in an aseptic work area, such as a laminar flow hood, using aseptic technique.
- Once the Pharmacy Bulk Package is punctured, it should not be removed from the aseptic work area during the entire 24 hour period of use.
- IV tubing and syringes used to administer Gadavist must be discarded at the conclusion of the radiological examination.
- The contents of the Pharmacy Bulk Package after initial puncture should be used within 24 hours. Discard any unused portion in accordance with regulations dealing with the disposal of such materials.

3 DOSAGE FORMS AND STRENGTHS

Gadavist is a sterile, clear, colorless to pale yellow solution for injection containing 1 mmol gadobutrol per milliliter (equivalent to 604.72 mg gadobutrol/mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30–59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60–89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following Gadavist administration to Bayer Healthcare (1-888-842-2937) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (for example, age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. 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 prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown *[see Clinical Pharmacology (12) and Dosage and Administration (2)]*.

5.2 Hypersensitivity Reactions

Anaphylactoid and anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred following Gadavist administration *[see Adverse Reactions (6)]*.

- 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.
- Administer Gadavist only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.

Most hypersensitivity reactions to Gadavist have occurred within half an hour after administration. Delayed reactions can occur up to several days after administration. Observe patients for signs and symptoms of hypersensitivity reactions during and following Gadavist administration.

5.3 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. Avoid intramuscular administration of Gadavist *[see Nonclinical Toxicology (13.2)]*.

6 ADVERSE REACTIONS

The most serious reactions to Gadavist are nephrogenic systemic fibrosis and hypersensitivity reactions *[see Warnings and Precautions (5.1 and 5.2)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect Gadavist exposure in 4549 subjects (4411 adults and 138 children aged 2–17) who received a dose that ranged from <0.09 to 0.51 mmol/kg body weight; the majority (n=2434) received the recommended dose of 0.1 (±0.01) mmol/kg body weight. Overall, 58.5% of the subjects were men and the ethnic distribution was 64.8% Caucasian, 27.3% Asian, 3% Hispanic, 1.3% Black, and 3.6% patients of other ethnic groups. The average age was 54.2 years (range from 2 to 93 years).

Overall, 4% of subjects reported one or more adverse reactions during a follow-up period that ranged from 24 hours to 7 days after Gadavist administration.

Adverse reactions associated with the use of Gadavist are usually mild to moderate in severity and transient in nature.

Table 1 lists adverse reactions that occurred in ≥0.1% subjects who received Gadavist.

Table 1: Adverse Reactions

Reaction	Rate (%) n=4549
Headache	1.5
Nausea	1.2
Injection site reactions	0.6
Dysgeusia	0.5
Feeling Hot	0.5
Dizziness	0.4
Vomiting	0.4
Rash (includes generalized, macular, papular, pruritic)	0.3
Pruritus (includes generalized)	0.2
Erythema	0.2
Dyspnea	0.2
Paresthesia	0.1

Adverse reactions that occurred with a frequency of <0.1% in subjects who received Gadavist include: hypersensitivity/anaphylactoid reactions (hypotension, urticaria, flushing, pallor), loss of consciousness, convulsion, parosmia, tachycardia, palpitation, dry mouth, malaise and feeling cold.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported during postmarketing use of Gadavist. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cardiac arrest
- Nephrogenic Systemic Fibrosis (NSF)
- Hypersensitivity/anaphylactoid reactions (anaphylactoid shock, circulatory collapse, blood pressure increased, chest pain, respiratory arrest, bronchospasm, cyanosis, oropharyngeal swelling, laryngeal edema, face edema, angioedema, conjunctivitis, eyelid edema, hyperhidrosis, cough, sneezing, and burning sensation) *[see Warnings and Precautions (5.2)]*

7 DRUG INTERACTIONS

There are no known drug interactions. Gadavist does not interfere with serum and plasma calcium measurements determined by colorimetric assays. Do not mix Gadavist with other drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Gadavist in pregnant women. While it is unknown if Gadavist crosses the human placenta, other gadolinium-based contrast agents (GBCAs) do cross the placenta in humans and result in fetal exposure. Limited published human data on exposure to other GBCAs during pregnancy did not show adverse effects in exposed neonates. Gadavist should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retardation of the embryonal development and embryolethality occurred in pregnant rats receiving maternally toxic doses of Gadavist (≥7.5 mmol/kg body weight) that were 12 times the human equivalent dose based on body surface area and in pregnant rabbits receiving doses (≥2.5 mmol/kg body weight) that were 8 times the recommended human dose (based on body surface area). In rabbits, this finding occurred without evidence of pronounced maternal toxicity and with minimal placental transfer (0.01% of the administered dose detected in the fetuses).

Gadavist was not teratogenic when given intravenously to monkeys during organogenesis at doses up to 8 times the recommended single human dose (based on body surface area) but was embryolethal at that dose. Because pregnant animals received repeated daily doses of Gadavist, their overall exposure was significantly higher than that achieved with the standard single dose administered to humans.

8.3 Nursing Mothers

It is not known whether gadobutrol is excreted in human milk. Limited case reports on use of GBCAs in nursing mothers indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in human breast milk. Studies have shown limited GBCA gastrointestinal absorption. Nonclinical data show that gadobutrol is excreted into breast milk in very small amounts (<0.1% of the dose intravenously administered) and the absorption via the gastrointestinal tract is poor (approximately 5% of the dose orally administered was excreted in the urine) *[see Clinical Pharmacology (12.3)]*. In lactating rats given 0.5 mmol/kg of intravenous [^{153}Gd]-gadobutrol, 0.01% of the total administered radioactivity was transferred to the neonate via maternal milk, mostly within 3 hours after the intravenous administration. Because many drugs are excreted in human milk, exercise caution when gadobutrol is administered to a nursing woman.

8.4 Pediatric Use

The pharmacokinetics, safety and efficacy of Gadavist at a single dose of 0.1 mmol/kg have been established in children 2 to 17 years of age. No dose adjustment according to age is necessary in this population. The safety and effectiveness of Gadavist have not been established in children below two years of age. *[See Dosage and Administration (2.1), Clinical Pharmacology (12.3).]*

8.5 Geriatric Use

In clinical studies of Gadavist, 1377 patients were 65 years of age and over, while 104 patients were 80 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, use of Gadavist in elderly patients should be cautious, reflecting the greater frequency of impaired renal function and concomitant disease or other drug therapy. No dose adjustment according to age is necessary in this population.

8.6 Renal Impairment

Prior to administration of Gadavist, screen all patients for renal dysfunction by obtaining a history and/or laboratory tests *[see Warnings and Precautions (5.1)]*. No dosage adjustment is recommended for patients with renal impairment.

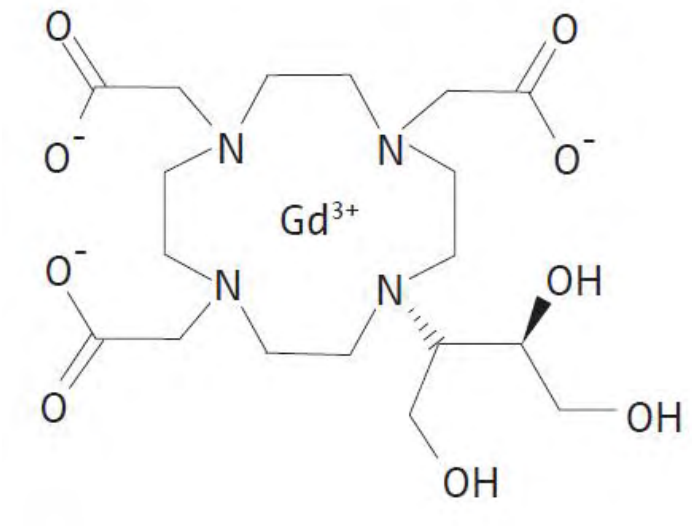
Gadavist can be removed from the body by hemodialysis *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The maximum dose of Gadavist tested in healthy volunteers, 1.5 mL/kg body weight (1.5 mmol/kg) (15 times the recommended dose), was tolerated in a manner similar to lower doses. Gadavist can be removed by hemodialysis *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Gadavist (gadobutrol) Injection is a paramagnetic macrocyclic contrast agent administered for magnetic resonance imaging. The chemical name for gadobutrol is 10–[(1SR,2RS)–2,3–dihydroxy–1–hydroxymethylpropyl]–1,4,7,10–tetraazacyclododecane–1,4,7–triacetic acid, gadolinium complex. Gadobutrol has a molecular formula of $C_{18}H_{31}GdN_4O_9$ and a molecular weight of 604.72.



Gadavist is a clear, colorless to pale yellow solution containing 1 mmol gadobutrol (equivalent to 604.72 mg gadobutrol) per mL as the active ingredient and the excipients calcobutrol sodium, trometamol, hydrochloric acid (for pH adjustment) and water for injection. Gadavist contains no preservatives.

The main physico-chemical properties of Gadavist (1 mmol/mL solution for injection) are listed below:

Osmolarity at 37°C (mOsm/L solution)	1117
Osmolality at 37°C (mOsm/kg H_2O)	1603
Viscosity at 37°C (mPa·s)	4.96
pH	6.6–8

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with:

- Differences in proton density
- Differences of the spin-lattice or longitudinal relaxation times (T_1)
- Differences in the spin-spin or transverse relaxation time (T_2)

When placed in a magnetic field, Gadavist shortens the T_1 and T_2 relaxation times. The extent of decrease of T_1 and T_2 relaxation times, and therefore the amount of signal enhancement obtained from Gadavist, is based upon several factors including the concentration of Gadavist in the tissue, the field strength of the MRI system, and the relative ratio of the longitudinal and transverse relaxation times. At the recommended dose, the T_1 shortening effect is observed with greatest sensitivity in T_1-weighted magnetic resonance sequences. In T2*-weighted sequences the induction of local magnetic field inhomogeneities by the large magnetic moment of gadolinium and at high concentrations (during bolus injection) leads to a signal decrease.

12.2 Pharmacodynamics

Gadavist leads to distinct shortening of the relaxation times even in low concentrations. At pH 7, 37°C and 1.5 T, the relaxivity (r_1) - determined from the influence on the relaxation times (T_1) of protons in plasma - is 5.2 L/(mmol·sec) and the relaxivity (r_2) - determined from the influence on the relaxation times (T_2) - is 6.1 L/(mmol·sec). These relaxivities display only slight dependence on the strength of the magnetic field. The T_1 shortening effect of paramagnetic contrast agents is dependent on concentration and r_1 relaxivity (see Table 2). This may improve tissue visualization.

Table 2: Relaxivity (r_1) of Gadolinium Chelates at 1.5 T

Gadolinium-Chelate	r_1 ($L \cdot mmol^{-1} \cdot s^{-1}$)
Gadobutrol	5.2
Gadoteridol	4.1
Gadobenate	6.3
Gadopentetate	4.1
Gadodiamide	4.3
Gadoversetamide	4.7

r_1 relaxivity in plasma at 37°C

Compared to 0.5 molar gadolinium-based contrast agents, the higher concentration of Gadavist results in half the volume of administration and a more compact contrast bolus.

Gadavist is a highly water-soluble, extremely hydrophilic compound with a partition coefficient between n-butanol and buffer at pH 7.6 of about 0.006.

12.3 Pharmacokinetics

Distribution

After intravenous administration, gadobutrol is rapidly distributed in the extracellular space. After a gadobutrol dose of 0.1 mmol/kg body weight, an average level of 0.59 mmol gadobutrol/L was measured in plasma 2 minutes after the injection and 0.3 mmol gadobutrol/L 60 minutes after the injection. Gadobutrol does not display any particular protein binding. In rats, gadobutrol does not penetrate the intact blood-brain barrier.

Metabolism

Gadobutrol is not metabolized.

Elimination

Gadobutrol is excreted in an unchanged form via the kidneys. Gadobutrol is eliminated from plasma with a mean terminal half-life of 1.81 hours (1.33–2.13 hours).

In healthy subjects, renal clearance of gadobutrol is 1.1 to 1.7 mL/(min·kg) and thus comparable to the renal clearance of inulin, confirming that gadobutrol is eliminated by glomerular filtration.

Within two hours after intravenous administration more than 50% and within 12 hours more than 90% of the given dose is eliminated via the urine. The extrarenal elimination is negligible.

Special populations

Gender

Gender has no clinically relevant effect on the pharmacokinetics of gadobutrol.

Geriatric

A single IV dose of 0.1 mmol/kg Gadavist was administered to 15 elderly and 16 non-elderly subjects. AUC was slightly higher and clearance slightly lower in elderly subjects as compared to non-elderly subjects *[see Use in Specific Populations (8.5)]*.

Pediatric

The pharmacokinetics of Gadavist were evaluated based on a population pharmacokinetic analysis in 130 pediatric subjects aged 2 to 17 years. Subjects received a single intravenous dose of 0.1 mmol/kg of Gadavist. The median AUC (mmol·h/L), clearance (L/hr/kg) and elimination half-life (hrs) of gadobutrol was similar across the age range of 2 – 17 years. The median AUC of gadobutrol in children 2 – 6 years (n=45) was 0.8 mmol·h/L, 1.0 mmol·h/L in children 7 – 11 years (n=39), and 1.2 mmol·h/L in children 12 – 17 years (n=46). The median clearance of gadobutrol in children 2 – 6 years was 0.13 L/hr/kg, 0.1 L/hr/kg in children 7 – 11 years, and 0.09 L/hr/kg in children 12 – 17 years, and the median elimination half-life of gadobutrol in children 2 – 6 years was 1.75 hours, 1.61 hours in children 7 – 11 years, and 1.65

hours in children 12 – 17 years. Approximately 99% (median value) of the dose was recovered in urine within 6 hours. *[See Use in Specific Populations (8.4).]*

Renal Impairment

In patients with impaired renal function, the serum half-life of gadobutrol is prolonged and correlated with the reduction in creatinine clearance.

After intravenous injection of 0.1 mmol gadobutrol/kg body weight, the elimination half-life was 5.8 ± 2.4 hours in mild to moderately impaired patients ($80>CL_{CR}>30$ mL/min) and 17.6 ± 6.2 hours in severely impaired patients not on dialysis ($CL_{CR} < 30$ mL/min). The mean AUC of gadobutrol in patients with normal renal function was 1.1 ± 0.1 mmol·h/L, compared to 4.0 ± 1.8 mmol·h/L in patients with mild to moderate renal impairment and 11.5 ± 4.3 mmol·h/L in patients with severe renal impairment.

Complete recovery in the urine was seen in patients with mild or moderate renal impairment within 72 hours. In patients with severely impaired renal function at least 80% of the administered dose was recovered in the urine within 5 days.

For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of Gadavist in order to enhance the contrast agent's elimination. Sixty-eight % of gadobutrol is removed from the body after the first dialysis, 94% after the second dialysis, and 98% after the third dialysis session. *[See Warnings and Precautions (5.1) and Use in Specific Populations (8.6).]*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies of gadobutrol have been conducted.

Gadobutrol was not mutagenic in *in vitro* reverse mutation tests in bacteria, in the HGPRT (hypoxanthine-guanine phosphoribosyl transferase) test using cultured Chinese hamster V79 cells, or in chromosome aberration tests in human peripheral blood lymphocytes, and was negative in an *in vivo* micronucleus test in mice after intravenous injection of 0.5 mmol/kg.

Gadobutrol had no effect on fertility and general reproductive performance of male and female rats when given in doses 12.2 times the human equivalent dose (based on body surface area).

13.2 Animal Toxicology and/or Pharmacology

Local intolerance reactions, including moderate irritation associated with infiltration of inflammatory cells was observed after paravenous administration to rabbits, suggesting the possibility of occurrence of local irritation if the contrast medium leaks around veins in a clinical setting *[see Warnings and Precautions (5.3)]*.

14 CLINICAL STUDIES

Patients referred for MRI of the central nervous system with contrast were enrolled in two clinical trials that evaluated the visualization characteristics of lesions. In both studies, patients underwent a baseline, pre-contrast MRI prior to administration of Gadavist at a dose of 0.1 mmol/kg, followed by a post-contrast MRI. In study A, patients also underwent an MRI before and after the administration of gadoteridol. The studies were designed to demonstrate superiority of Gadavist MRI to non-contrast MRI for lesion visualization. For both studies, pre-contrast and pre-plus-post contrast images (paired images) were independently evaluated by three readers for contrast enhancement and border delineation using a scale of 0 to 4, and for internal morphology using a scale of 0 to 3 (Table 3). Lesion counting was also performed to demonstrate non-inferiority of paired Gadavist image sets to pre-contrast MRI. Readers were blinded to clinical information.

Table 3: Primary Endpoint Visualization Scoring System

Score	Visualization Characteristics		
	Contrast Enhancement	**Border Delineation**	**Internal Morphology**
1	None	None	Poorly visible
2	Weak	Moderate	Moderately visible

3	Clear	Clear but incomplete	Sufficiently visible
4	Clear and bright	Clear and complete	N/A

Diagnostic efficacy was determined in 657 subjects. The average age was 49 years (range 18 to 85 years) and 42% were male. The ethnic representations were 39% Caucasian, 4% Black, 16% Hispanic, 38% Asian, and 3% of other ethnic groups.

Table 4 shows a comparison of visualization results between paired images and pre-contrast images. Gadavist provided a statistically significant improvement for each of the three lesion visualization parameters when averaged across three independent readers for each study.

Table 4: Visualization Endpoint Results of Central Nervous System Adult MRI Studies with 0.1 mmol/kg Gadavist

Endpoint	**Study A N=336**			**Study B N=321**		
	Pre-contrast	Paired	Difference*	Pre-contrast	Paired	Difference
Contrast Enhancement	0.97	2.26	1.29^	0.93	2.86	1.94^
Border Delineation	1.98	2.58	0.60^	1.92	2.94	1.02^
Internal Morphology	1.32	1.93	0.60^	1.57	2.35	0.78^
Average # Lesions Detected	8.08	8.25	0.17**	2.65	2.97	0.32^^

* Difference of means = (paired mean) – (pre-contrast mean)
^ $p<0.001$
^^ Met noninferiority margin of -0.35
** Did not meet noninferiority margin of -0.35

Performances of Gadavist and gadoteridol for visualization parameters were similar. Regarding the number of lesions detected, study B met the prespecified noninferiority margin of -0.35 for paired read versus pre-contrast read while in Study A, Gadavist and gadoteridol did not.

For the visualization endpoints contrast enhancement, border delineation, and internal morphology, the percentage of patients scoring higher for paired images compared to pre-contrast images ranged from 93% to 99% for Study A, and 95% to 97% for Study B. For both studies, the mean number of lesions detected on paired images exceeded that of the pre-contrast images; 37% for Study A and 24% for Study B. There were 29% and 11% of subjects in which the pre-contrast images detected more lesions for Study A and Study B, respectively.

The percentage of patients whose average reader mean score changed by ≤ 0, up to 1, up to 2, and ≥ 2 scoring categories presented in Table 3 is shown in Table 5. The categorical improvement of (≤ 0) represents higher (< 0) or identical ($= 0$) scores for the pre-contrast read, the categories with scores > 0 represent the magnitude of improvement seen for the paired read.

Table 5: Primary Endpoint Visualization Categorical Improvement for Average Reader

	Study A N=336				**Study B N=321**			
Endpoint	**Categorical Improvement (Paired – Pre-Contrast) %**				**Categorical Improvement (Paired – Pre-Contrast) %**			
	≤0	>0 – <1	1 – <2	≥2	≤0	>0 – <1	1 – <2	≥2
Contrast Enhancement	1	30	55	13	3	6	34	57
Border Delineation	7	73	18	1	5	38	51	5
Internal Morphology	4	79	17	0	5	61	33	1

For both studies, the improvement of visualization endpoints in paired Gadavist images compared to pre-contrast images resulted in improved assessment of normal and abnormal CNS anatomy.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gadavist is a clear, colorless to pale yellow solution containing 1 mmol gadobutrol per milliliter (equivalent to 604.72 mg gadobutrol) per mL. Gadavist Pharmacy Bulk Packages are supplied in the following sizes:

30 mL Pharmacy Bulk Package, rubber stoppered in cartons of 5, Boxes of 10 (NDC 50419-325-14)

65 mL Pharmacy Bulk Package, rubber stoppered, Boxes of 10 (NDC 50419-325-15)

16.2 Storage and Handling

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Should freezing occur, Gadavist should be brought to room temperature before use. If allowed to stand at room temperature, Gadavist should return to a clear, colorless to pale yellow solution. Visually inspect Gadavist for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored, if particulate matter is present or if the container appears damaged.

17 PATIENT COUNSELING INFORMATION

17.1 Nephrogenic Systemic Fibrosis

Instruct patients to inform their physician if they:

- Have a history of kidney disease and/or liver disease, or
- Have recently received a GBCA

GBCAs increase the risk of NSF among patients with impaired elimination of drugs. To counsel patients at risk of NSF:

- Describe the clinical manifestation of NSF
- Describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following Gadavist administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

17.2 Common Adverse Reactions

Inform patients that they may experience:

- Reactions along the venous injection site, such as mild and transient burning or pain or feeling of warmth or coldness at the injection site
- Side effects of headache, nausea, abnormal taste and feeling hot

17.3 General Precautions

Instruct patients receiving Gadavist to inform their physician if they:

- Are pregnant or breastfeeding
- Have a history of allergic reaction to contrast media, bronchial asthma or allergic respiratory disorder,
- Are taking any medications

Manufactured for:

Bayer HealthCare
Pharmaceuticals

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Manufactured in Germany

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