



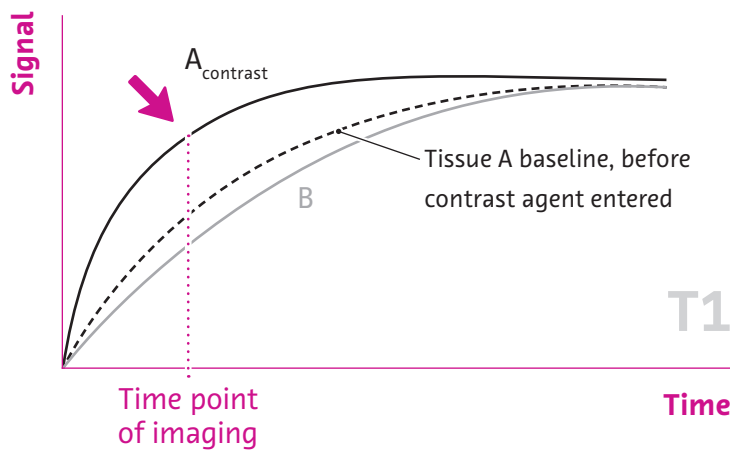
Relaxivity Matters

Clear Direction.  From Diagnosis to Care.

Gadovist® 1.0
Gadobutrol

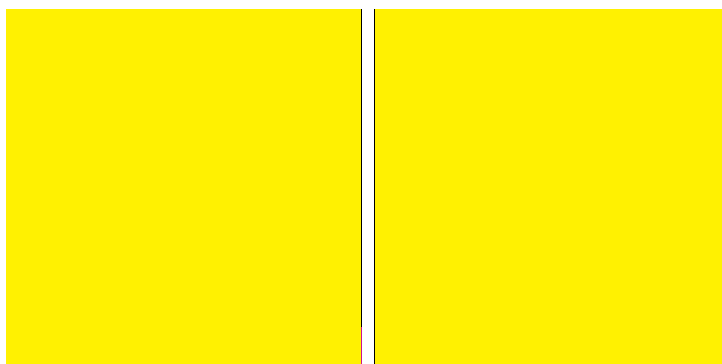
What Is Relaxivity?

- ✓ The effect of a gadolinium-based contrast agent (GBCA) to generate contrast mainly depends on its local tissue concentration and relaxivity.¹
- ✓ Relaxivity is a marker for the ability of a GBCA to enhance signal intensity on the MR image and is a prerequisite of technical efficacy of GBCAs.²



Signal enhancement by contrast media. The contrast agent only entered tissue A but did not enter tissue B.³

Adapted from Schild HH. MRI Made Easy... well almost [iOS App]. Version 1.5.1. Utrecht, The Netherlands: BestApps BV; 2018

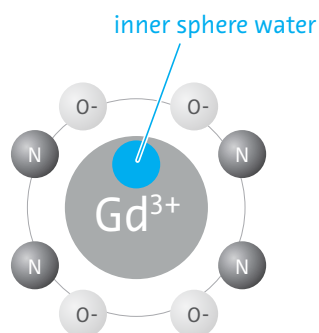


T1-weighted image without GBCA (1), T1-weighted image with GBCA (2).

Images courtesy of PD Dr. med. Alexander Huppertz, Klinikum Ernst von Bergmann, Potsdam, Germany

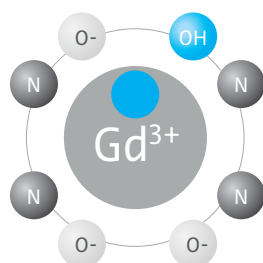
Molecular Structure Influences Relaxivity

- ✓ High relaxivity can be generated by additional hydroxy groups leading to better interaction with bulk water and higher water exchange rates⁴⁻⁶



Gadoterate meglumine

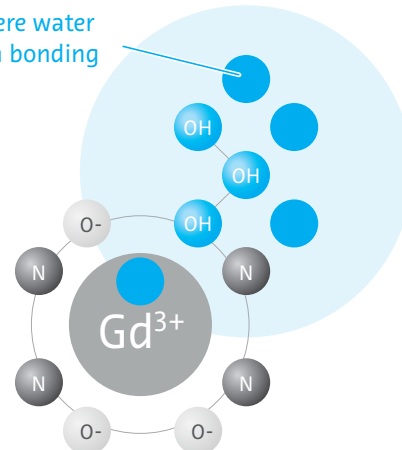
A) **3.6** (3.4–3.8)
B) **3.89** (± 0.14)



Gadoteridol

A) **4.1** (3.9–4.3)
B) **4.32** (± 0.5)

second sphere water
by hydrogen bonding



Gadovist®/Gadobutrol

A) **5.2** (4.9–5.5)
B) **4.58** (± 0.18)

T1 relaxivity ($L \text{ mmol}^{-1} \text{ s}^{-1}$) at 1.5T in A) bovine plasma at 37°C (based on Rohrer M et al. 2005)⁷, B) human whole blood at 37°C (based on Shen Y et al. 2015)⁸

➤ High relaxivity due to molecular properties of Gadovist^{®5,7}

Relaxivity of Gadovist® Compared to Other Macrocylic GBCAs



While the absolute relaxivity values differ from study to study due to different measurement conditions, the order of relaxivity values is consistent between studies⁷⁻⁹

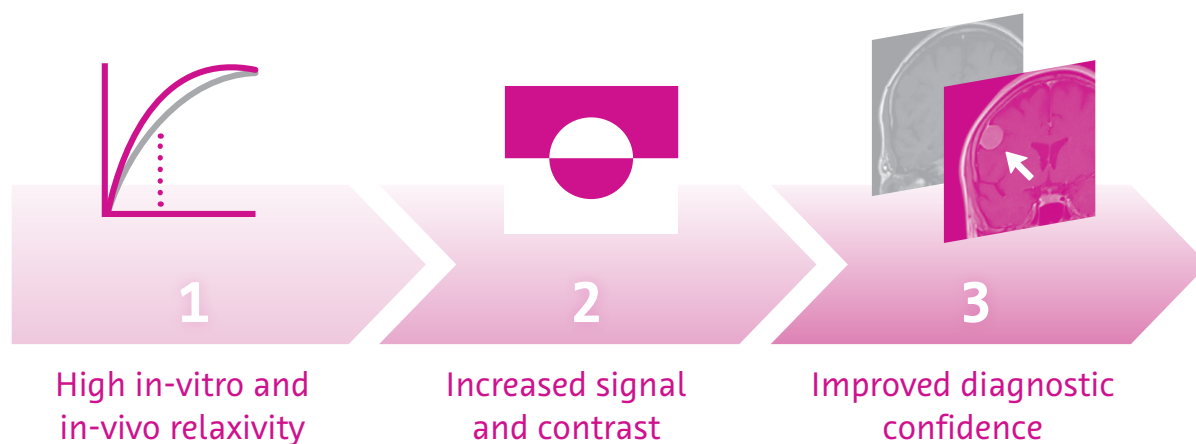
➤ Gadovist® shows consistently high relaxivity values



Why Is Relaxivity Important?

- ✓ Higher relaxivity could result in*
 - increased signal on T1-weighted images^{10,11}
 - enhanced image quality¹¹
 - improved diagnostic confidence^{12,13}
- ✓ In steady-state imaging, GBCA distribution in tissue** and imaging time point contributes to signal enhancement: higher relaxivity leads to higher signal increase¹
- ✓ In dynamic imaging (e.g. MRA), the image is obtained while the GBCA passes through a certain area: local tissue concentration, injected dose and relaxivity impact the signal^{14,15}

Relationship between higher relaxivity and improved image quality and diagnostic confidence in three steps^{10,11,16}



* at equal contrast dose

** e.g. leakage due to blood brain barrier disruption or vascularization



How to Investigate the Clinical Effect of Relaxivity

- ✓ Direct comparison studies have been conducted to investigate the effect of the high relaxivity of Gadovist® vs. the other macrocyclic GBCAs gadoteridol and gadoterate meglumine
- ✓ Injected dose and imaging parameters need to be kept identical in intra-individual trials when investigating possible effects of relaxivity differences between two GBCAs

➤ In 3 out of 4 direct comparison trials, Gadovist® showed a higher signal intensity and better detection, delineation and characterization vs. gadoteridol in CE CNS MRI.^{12,13,17,18}

➤ In 2 out of 3 direct comparison trials, Gadovist® showed a higher signal intensity and better detection, delineation and characterization vs. gadoterate meglumine in CE CNS MRI.¹⁹⁻²¹

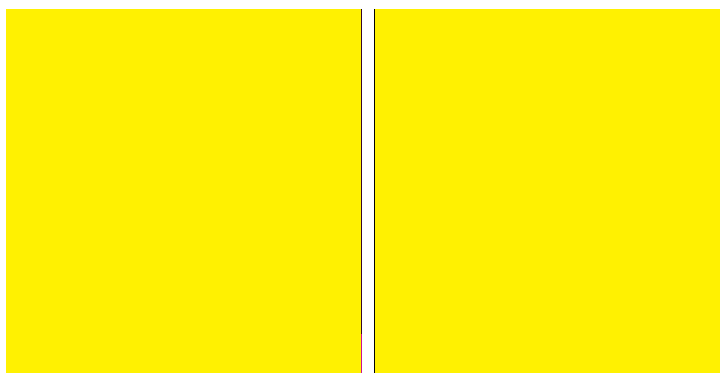
➤ In 4 out of 4 direct intra-individual comparison trials, Gadovist® led to a higher signal increase in MRA and 3 out of those 4 showed an overall preference of Gadovist® vs. gadoterate meglumine.^{15,22-24}

Comparison Studies CNS

> Gutierrez JE et al. 2015 – A prospective, multicenter, randomized, double-blind, intra-individual comparison study.

Gadovist® Demonstrates Greater CE, Improved Sensitivity and Accuracy for Detection of Malignant Disease vs. Gadoteridol in CNS¹²

- ✓ Improved differentiation of malignant vs. benign lesions attributed to higher relaxivity of Gadovist®
- ✓ Gadovist® shows significantly higher sensitivity and accuracy for detection of malignancy compared to gadoteridol without change in specificity.



Gadovist®

Gadoteridol

Follow-up evaluation for a glioma diagnosis.

- 1 Gadovist® contrast-enhanced T1w image showed enhancement with sharp delineation of the anatomic involvement, which was diagnosed as residual / recurrent high-grade glial tumor.
- 2 Gadoteridol contrast-enhanced T1w image shows less sharp rings of enhancement that were characterized as infection rather than tumor.

	Gadovist®	Gadoteridol	Nominal P-value
Sensitivity (n = 93)	66.7 %	60.2 %	P = 0.014
Specificity (n = 199)	97.5 %	97.5 %	P = 1.000
Accuracy (n = 292)	87.7 %	85.6 %	P = 0.034

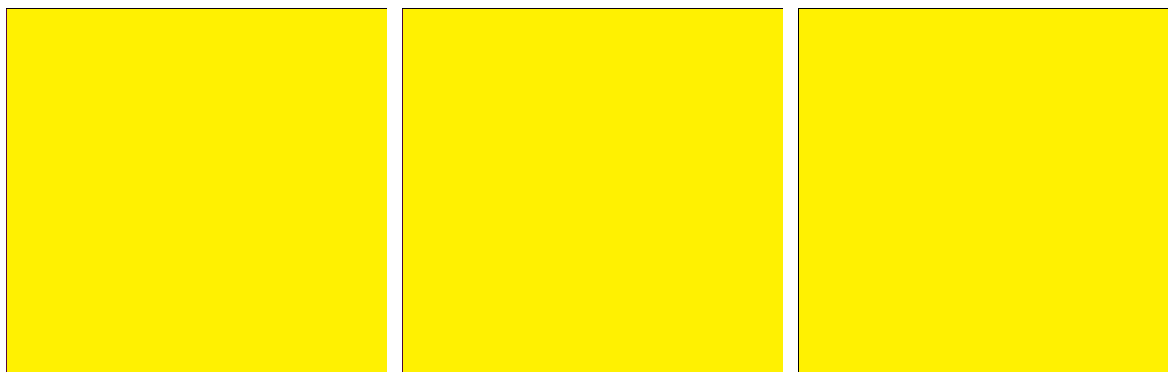
Sensitivity, specificity, and accuracy in determination of malignancy for combined Gadovist® contrast-enhanced vs. combined gadoteridol contrast-enhanced imaging (majority reader diagnosis). Full analysis set (n = 336).

> “Increase in diagnostic performance may be a result of improved enhancement in poorly enhancing malignant lesions”

➤ **Katakami N et al. 2011** – A phase II/III, multicenter, single-blind, randomized, controlled, crossover, intra-individual comparison study.

Gadovist® Shows Improvement for Radiosurgery Planning vs. Gadoteridol¹³

Image Contrast



Gadovist® 0.1 mmol/kg b.w.

Gadovist® 0.2 mmol/kg b.w.

Gadoteridol 0.2 mmol/kg b.w.

Performance in Stereotactic Radiosurgery Planning

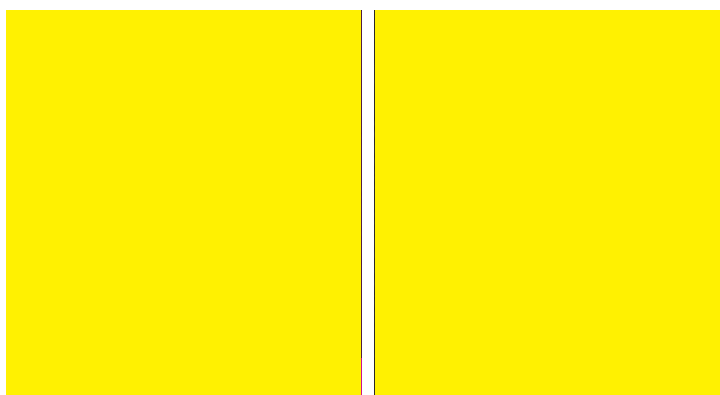
0.2 mmol/kg gadoteridol vs. dose of Gadovist®	0.1 mmol/kg b.w. # patients (%)	0.2 mmol/kg b.w. # patients (%)
Gadovist® better than gadoteridol	26/65 (40.0)	22/62 (36.5)
Gadoteridol better than Gadovist®	15/65 (23.1)	10/62 (16.1)
Both agents the same	24/65 (36.9)	30/62 (48.4)

➤ Single dose of Gadovist® was shown to be non-inferior to a double dose of gadoteridol at detecting brain metastases, and could be effectively used for treatment planning

> **Koenig M et al. 2013** – A prospective, single-center, randomized, intra-individual comparison study.

Significantly Superior CE Characteristics For Gadovist® in Primary and Secondary Brain Tumors¹⁸

- ✓ Intra-individual comparison showed preference of gadobutrol over gadoteridol
- ✓ Quantitative results demonstrated significant superiority in lesion-to-brain contrast



Gadovist®

Gadoteridol

A 49-year-old male patient with metastasis of laryngeal squamous cell carcinoma. T1-weighted SE images after Gadovist® (1) and gadoteridol (2). There is a higher T1 signal with Gadovist® leading to a better enhancement of the tumor margin follow-up evaluation for a glioma diagnosis.

Significantly superior contrast in a routine MRI protocol

Overall preference (FAS**), N = 51	Reader 1, N (%)	Reader 2, N (%)
	P = 0.0046	P = 0.002
Gadovist® better than gadoteridol	36/51 (71 %)	34/51 (67 %)*
Gadoteridol better than Gadovist®	15/51 (29 %)	9/51 (18 %)*

Adapted from Koenig M, et al. 2013¹⁸

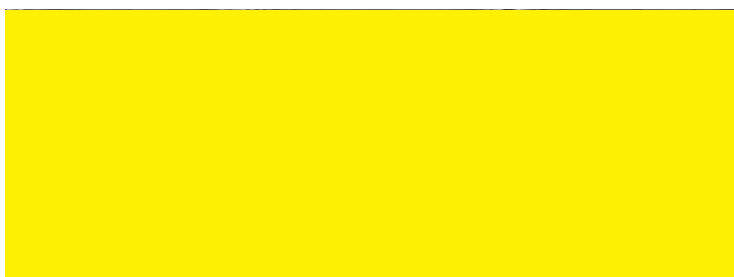
* N = 8 were rated with no preference; ** Full analysis set

➤ **Anzalone N et al. 2013** – A prospective, multicenter, randomized, open-label, intra-individual comparison study.

Better Visualization of Enhancing Brain Lesions by Gadovist® vs. Gadoterate Meglumine²⁰



Gadoterate meglumine



Gadovist®

A 69-year-old male patient with butterfly glioma (glioblastoma WHO grade IV). Three consecutive T1-weighted images after a single dose (0.1 mmol/kg body weight) of gadoterate meglumine (1) and Gadovist® (2).

Overall preference*	# assessments (%)
Gadovist® better than gadoterate meglumine	131/199** (66)
Gadoterate meglumine better than Gadovist®	68/199** (34)

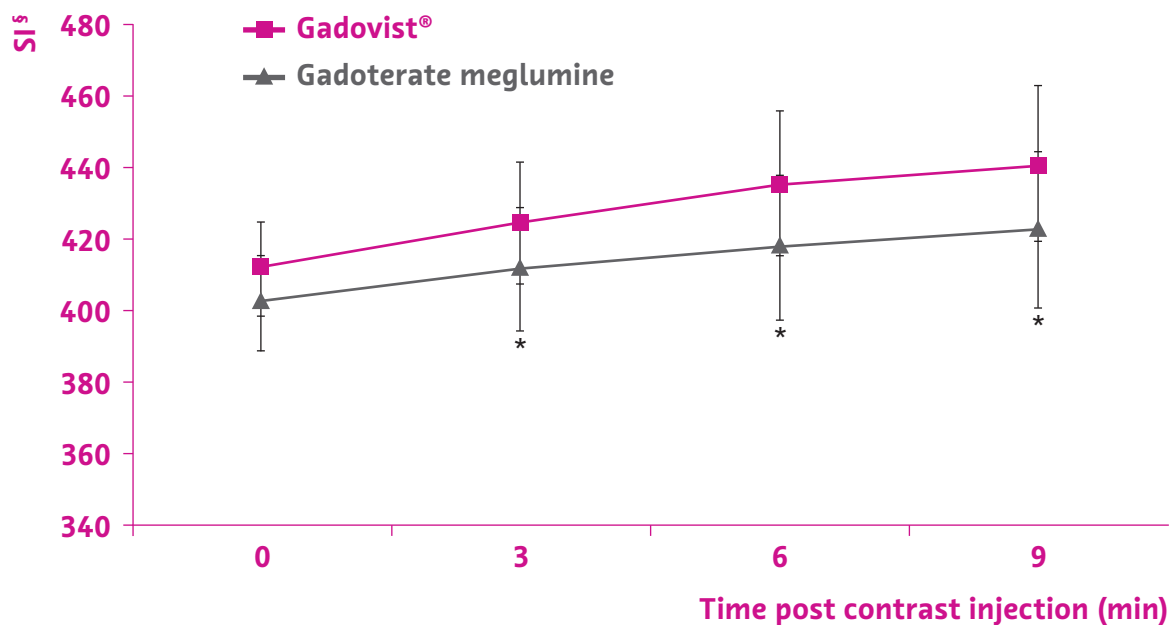
* Three independent blinded readers assessed off-site their overall diagnostic preference (primary efficacy parameter) based on a matched pairs approach.
 ** Assessments in which a preference for either agent was expressed (P<0.001). No preference recorded in a further 175.

Gadovist® provided

- Better contrast enhancement of lesions than gadoterate meglumine (P<0.001)
- Higher lesion-to-brain signal (P<0.001)
- 9% difference in relative enhancement (P<0.001)

➤ **Saake M et al. 2016** – A prospective, multicenter, randomized, intra-individual comparison study.

Increased Enhancement in MS Lesions With Gadovist® vs. Gadoterate Meglumine²¹



Measured SI of MS lesions after GBCA injection. Asterisk indicates statistically significant difference ($p < 0.05$). Bars show standard deviations. Gadovist® generated higher lesion SI at all time points.

- Significantly higher mean lesion enhancement for Gadovist® ($p = 0.05$)
- Subjective preference showed non-significant tendency in favor of Gadovist®

⁵ SI = Signal Intensity

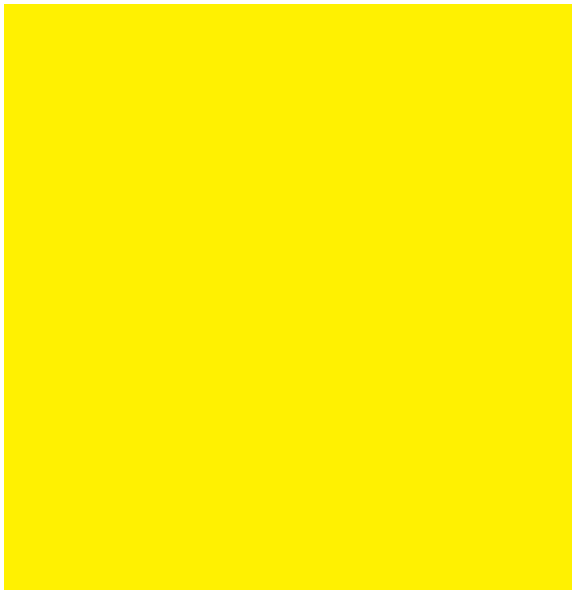
Comparison Studies MR Angiography



➤ **Hoelter P et al. 2017** – A prospective, single-center, randomized, intra-individual comparison study.

Higher Enhancement in Cervical and Intracranial MRA²⁴

- ✓ Significantly higher signal-to-noise (SNR) ratio ($p = 0.032$) and contrast to noise (CNR) ratio ($p = 0.031$) for Gadovist® compared to gadoterate meglumine
- ✓ Significantly better delineation of the M1/M2 segments for Gadovist® ($p = 0.041$)
- ✓ Overall preference was given to Gadovist® ($p = 0.02$)



MRA with high quality M1 (white arrow)/ M2 segment (grey arrow) depiction of MCA after injection of Gadovist®.

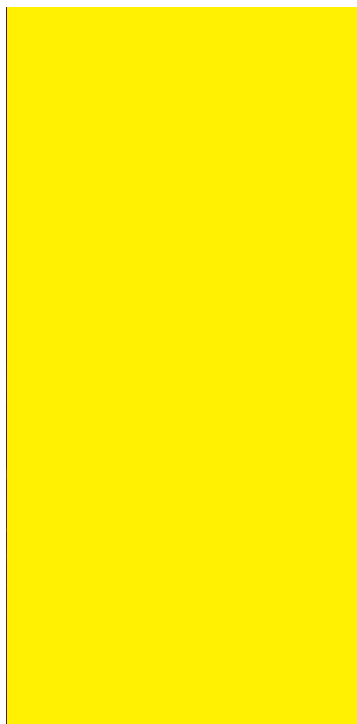
➤ “Improved assessment of vasculature in CVD patients with Gadovist®”



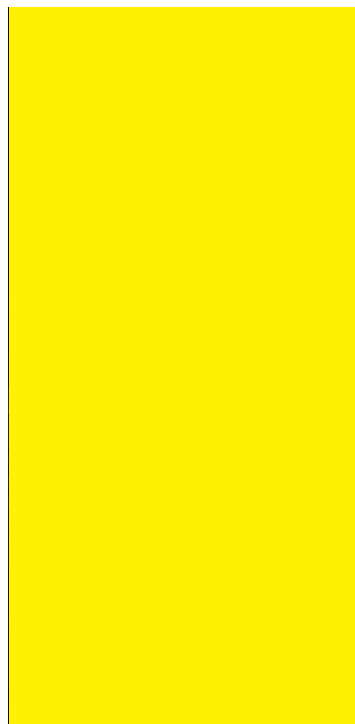
> Kramer JH et al. 2013 – A prospective, single-center, randomized, intra-individual comparison study.

Gadovist® Shows Higher SNR and CNR in MRA of Supra-Aortic Vessels¹⁵

- ✓ Significantly higher SNR and CNR for Gadovist® compared to gadoterate meglumine
- ✓ High image quality for static and dynamic carotid MRA



Gadovist®



Gadoterate meglumine

Higher image quality with equimolar dose in MRA

Examples of the static MRA examinations acquired with Gadovist® (1), and gadoterate meglumine (2). Note the already visually assessable differences in signal intensity and image contrast.



Summary

- ✓ With its high relaxivity, Gadovist® leads to a higher signal intensity and contrast in CNS MRI than gadoterate meglumine and gadoteridol enabling better detection, delineation and characterization of CNS lesions.^{7-9,12,13,18,20,21}
- ✓ The high relaxivity of Gadovist® combined with the 1-molar concentration can lead to higher SNR and CNR in CE MRA vs. gadoterate meglumine^{15,22-24}

➤ Gadovist® contrast-enhanced CNS MRI and MRA can lead to a higher diagnostic confidence both at 1.5T and 3T via better image quality and higher sensitivity/specificity.^{7-9,12,13,15,18,20-24}





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ABBREVIATED PRESCRIBING INFORMATION

Brand name of product: Gadovist 1.0 mmol/ml solution for injection. **Approved name of the active ingredient:** Each ml contains 1.0 mmol gadobutrol (equivalent to 604.72 mg gadobutrol). **Indications:** Gadovist is indicated in adults and children of all ages including term neonates for contrast enhanced whole body magnetic resonance imaging (MRI) including: Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI); Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesion to classify these lesions as benign or malignant; Contrast enhancement in Magnetic Resonance Angiography (CE-MRA); MR Imaging of pathologies of the whole body. It facilitates visualization of abnormal structures or lesions and helps in the differentiation between healthy and pathological tissue. **Dosage and method of administration:** Dosage depends on indication. A single intravenous injection of 0.1 mmol gadobutrol per kg body weight (equivalent to 0.1 ml Gadovist per kg body weight) is generally sufficient. A total amount of 0.3 mmol gadobutrol per kg body weight (equivalent to 0.3 ml Gadovist per kg body weight) may be administered at maximum. Whole body MRI (except MRA): In general, the administration of 0.1 ml Gadovist per kg body weight is sufficient to answer the clinical question. **Contraindications:** There are no absolute contraindications to the use of Gadovist. **Special warnings and special precautions for use:** *Hypersensitivity:* Particularly careful risk-benefit assessment is required in patients with known hypersensitivity to Gadovist. *Impaired renal function:* Prior to administration of Gadovist all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests. *Seizure disorders:* As with other gadolinium-chelate-containing contrast media, special precaution is necessary in patients with a low threshold for seizures. **Undesirable effects:** The most frequently observed adverse drug reactions ($\geq 0.5\%$) in patients receiving Gadovist are headache, nausea and dizziness. **For further prescribing information, please contact:** Bayer Co. (M) Sdn Bhd, B-19-1 & B-19-2, The Ascent Paradigm, No. 1, Jalan SS 7/26A, Kelana Jaya, 47301 Petaling Jaya, Selangor. **Date of revision :** 08 Nov 2016

Subject to medical prescription.

For healthcare professional only

Clear Direction.  From Diagnosis to Care.

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Bayer Co. (Malaysia) Sdn Bhd
B-19-1 & B-19-2, The Ascent Paradigm
No. 1, Jalan SS 7/26A, Kelana Jaya, 47301 Petaling Jaya, Selangor
Tel: +603 7801 3088 Fax: +603 7886 3338 www.bayer.com

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