

# Overview on the efficacy and safety of gadobutrol: an MRI contrast agent for the CNS, body and vessels

Contrast-enhanced MRI has become a mainstay of clinical imaging with unlimited applications. However, a limitation of conventional contrast agents in MRI is the insufficient signal-to-noise ratios due to relaxivity. Gadobutrol (1.0 mmol/ml), an extracellular macrocyclic contrast agent of high stability, is indicated for contrast-enhanced MRI of adults, adolescents and children 2 years of age and older. Gadobutrol offers increased  $T_1$  relaxivity, which improves MR image quality and clinical use of the technique.

**KEYWORDS:** contrast-enhanced MRA • contrast-enhanced MRI • CNS • Gadavist™ • gadobutrol • gadolinium-based contrast agent • Gadovist™ • kidney • liver

The use of gadolinium-based contrast agents (GBCAs) to improve MRI has been well established for over 20 years [1,2]. Unenhanced MRI of the CNS, abdomen/pelvis, breast and vascular system has mainly been used to display/demarcate focal pathologies or areas of stenosis; however, GBCAs have improved the detection, characterization and visualization of lesions involved in such pathologies, improving the diagnostic work-up, therapy planning and monitoring evolution after therapeutic interventions [3]. Thus, when any lesion located in this body area are clinically suspected, combined MRI with and without GBCAs is the best method for defining lesion characteristics.

Gadobutrol is a nonionic, macrocyclic, extracellular MRI contrast agent. Like gadopentetate dimeglumine (MAGNEVIST® Bayer-Schering, Berlin, Germany) and other extracellular MRI contrast agents, gadobutrol contains gadolinium ions (Gd;  $Gd^{3+}$ ). Gadolinium is a rare earth element that causes contrast enhancement in MRI scans. Gadobutrol is the active ingredient, it is a paramagnetic gadolinium chelate with low osmolality and viscosity, and high paramagnetic effect (relaxivity) [4], the Gd is tightly bound in a macrocyclic complex with a high stability. The relevant stability parameter for macrocyclic contrast agents in contrast to open-chain GBCAs is kinetic stability instead of thermodynamics. A study in 2006 examined the stability of different compounds by using possible transmetallation by zinc ions and calculated a so-called 'long time index' and 'ratio index'. The ratio index, for example, showed a decomplexation of less than 10% after 5000 min, compared with 70–600 min for the open-chain compounds [5].

As with other GBCAs, the paramagnetic qualities of the gadolinium ion shortens the  $T_1$  relaxation times of nearby water protons and results in increased signal on  $T_1$ -weighted images improving the lesion detection (sensitivity), characterization (specificity) and staging. Besides the registered trade name (GADAVIST® Injection, USA and GADOVIST®, in the rest of the world, the generic name (gadobutrol) and the laboratory nomenclature (Gd-DO3A-butriol or ZK 135079) have been used in some publications. Due to the unique physicochemical qualities of gadobutrol, solutions of 1.0 M concentration of Gd can be prepared. This concentration is twice that of all other extracellular MRI contrast media currently marketed (0.5 M).

At the same dose as 0.5 M agents, injected intravenously at the same rate, the 1.0 M concentration results in higher first-pass concentrations than a 0.5 M formulation [6]. In brain perfusion MRI, these improved bolus characteristics of 1.0 M gadobutrol were studied to evaluate the differences in contrast between ischemic and nonischemic tissue as compared with the 0.5 M concentration at the same dose [7]. Furthermore, gadobutrol is known to provide similar imaging properties in conventional contrast-enhanced MRI (CE-MRI) of various body regions other than the CNS, as is the case with other approved contrast agents. Gadobutrol is suitable for all clinically used MRI sequences (e.g., imaging of focal disease in different body regions) without the need to modify the parameters used with other GBCAs, as the concentration of the contrast agent has no significant impact on the extracellular distribution including the distribution in lesions.

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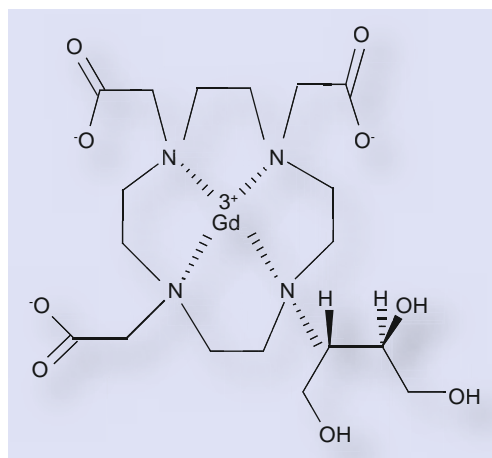
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**Figure 1. Gadobutrol chemical structure (racemic).**

Thus, gadobutrol can provide diagnostic information to classify benign and malignant lesions independent of the body region under examination.

### Overview of the market

MRI is currently used for a wide range of clinical applications and is not limited to specific body areas. In the majority of cases, extracellular contrast agents are used to improve the diagnostic information in terms of lesion detection, localization and differentiation between benign and malignant lesions. Some more targeted MR contrast agents exist that either are blood-pool agents with a strong protein binding affinity for MR angiography (MRA) [8], or hepatocyte-specific agents like gadoxetate (Eovist® Bayer-Schering, Berlin, Germany, synonym Primovist®) or MultiHance® (Bracco Diagnostics Inc., NJ, USA) for liver MRI [9]. In general, the clinical usefulness of extracellular contrast agents for various applications

to detect or exclude a disease has been documented by their approval for imaging areas all over the body. The contribution of a CE-MRI is commonly accepted in the medical–scientific community. It can lead to a change in the diagnostic work-up, differential diagnosis and patient management [6,7,10]. The first approval of a GBCA occurred in 1988 and has since led to the performance of more than 160 million CE-MRI examinations worldwide.

Advances in hardware and software have created additional needs regarding high relaxivity and/or small volumes of MRI contrast media, especially in perfusion MRI and MRA with rapid image acquisition. Particularly in dynamic first-pass MRI studies, a tight bolus (i.e., a short-lasting bolus containing a high concentration of contrast agent) is a prerequisite for good visualization [11]. A highly concentrated contrast agent like gadobutrol is ideal for such applications, resulting in high transitory Gd concentrations in the area of interest, for example, in brain perfusion MRI and dynamic contrast-enhanced MR angiography (CE-MRA).

### Introduction to the compound

Gadobutrol is an electrically neutral gadolinium-containing contrast agent from a family of macrocyclic compounds. Gadobutrol was designed to give radiologists an additional option of an MRI contrast agent with high relaxivity and a potential higher capacity to provide contrast in areas of interest.

### Chemistry

The chemical name for Gadovist is [10-[2,3-dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato-(3-)-N1,N4,N7,N10,O1,O4,O7] gadolinium (FIGURE 1). It has a molecular weight of 604.72 g/mole. It has a pK value of less than 2.0 (conjugate acid) and a pH value of 6.0–8.0, and it is freely soluble in water. Gadobutrol is a nonionic injectable contrast medium for use in MRI. It is provided as a sterile, clear, colorless and pyrogen-free aqueous, 0.5 or 1.0 mol/l solution, which is ready for use.

### Pharmacodynamics

The signal intensity and contrast on MR images is determined by the water content and the behavior of the water protons in the magnetic field applied by the scanner, and the characteristic parameters for this are: the (proton) relaxation times ( $T_1$  and  $T_2$ ); due to

**Table 1. Pharmacokinetic characteristics of gadobutrol.**

Pharmacokinetic characteristic	1.0 M gadobutrol mean (SD)
Dose (mmol/kg bodyweight)	0.1
AUC norm ( $\mu\text{mol}\cdot\text{h/l}$ )	1074 (95.9)
$t_{1/2p}$ , $\beta$	1.78 (0.43)
$V_{ss}$ (l/kg)	0.21 (0.02)
Cl (ml/mg/min)	1.56 (0.15)
CLR (ml/mg/min)	1.56 (0.18)
Urine, 72 h PI (% of dose)	100.3 (2.60)
Urine, 12 h PI (% of dose)	98.0 (3.33)
Feces, 72 h PI (% of dose)	0.04 (0.02)
Recovery (% of dose)	100.3 (2.60)

AUC: Area under curve; Cl: Total clearance; CLR: Renal clearance; SD: Standard deviation;  $t_{1/2p}$ : Half-life;  $V_{ss}$ : Volume of distribution at steady state.  
Data taken from [12].

Table 2. Number of patients by indication and dose in the Phase II–IV studies.

Indication	n
CNS indications (cranial and spinal MRI, brain perfusion)	2448
Other 'body' areas	1139
Contrast-enhanced MR angiography	754
Myocardial perfusion	226
Pediatric patients	138
Total	4705

some inherent differences in these parameters between normal tissue and pathological states (e.g., lesions), water content is higher and relaxation times are shorter, these differences allow normal tissue and lesions to be differentiated. However, if the differences in these parameters are low or there is no difference, no delineation of organs, tissues and lesions is feasible.

The use of the contrast agent causes enhancement of organs, tissues and lesions on MR images by shortening the relaxation times  $T_1$  and  $T_2$ . Since gadobutrol shortens the relaxation times of tissues, it enables enhanced delineation of organs, tissues and lesions. This characteristic parameter for the potential (strength) of an MR contrast agent is called relaxivity. The relaxivity values of gadobutrol under clinically relevant conditions (in plasma, 37°C and at 1.5 T) are high (i.e., the relaxivity  $[r_1]$  is about 5.2 l/[mmol\*s] and the relaxivity  $[r_2]$  is about 6.1 l/[mmol\*s]) [4]. In combination with the unique 1 M formulation, gadobutrol has the highest effect on relaxation times per milliliter of drug product formulation, compared with all other extracellular contrast agents. The effect on the relaxation times in tissues, and consequently the signal intensity and contrast on the MR images, is dependent on the relaxivity and the concentration of the contrast agent in the area of interest. Gadobutrol improves the detection and visualization of specific features of pathological states (e.g., lesions) by showing:

abnormal vascularity (called first-pass imaging as the contrast agent is still in the vessel within the first seconds after administration); leaking through a disrupted blood barrier; or being distributed into the extracellular space, thereby increasing the contrast enhancement of a lesion or displaying vessel structures.

### Pharmacokinetics & metabolism

Gadobutrol has first-order pharmacokinetics in the body. After single intravenous administration, gadobutrol rapidly distributes into the extracellular space followed by fast renal elimination of the unchanged drug. The concentrations in plasma decrease in a biphasic manner characterized by an early distribution phase during the first minutes, followed by a second phase governed by elimination from plasma. Protein binding of gadobutrol is negligible [12].

The renal clearance (CLR) is almost identical to the total clearance and mainly attributed to glomerular filtration, since the CLR is similar to the clearance of creatinine. Gadobutrol is excreted from the kidneys unchanged, and eliminated from plasma with a mean half-life of 1.81 h (1.33–2.13 h). In healthy subjects, CLR of gadobutrol is 1.1–1.7 ml/min/kg, which is almost identical to the total clearance and thus comparable to the CLR of inulin, confirming that gadobutrol is eliminated by glomerular filtration. Within 2 and 12 h after intravenous administration, more than 50 and 90%

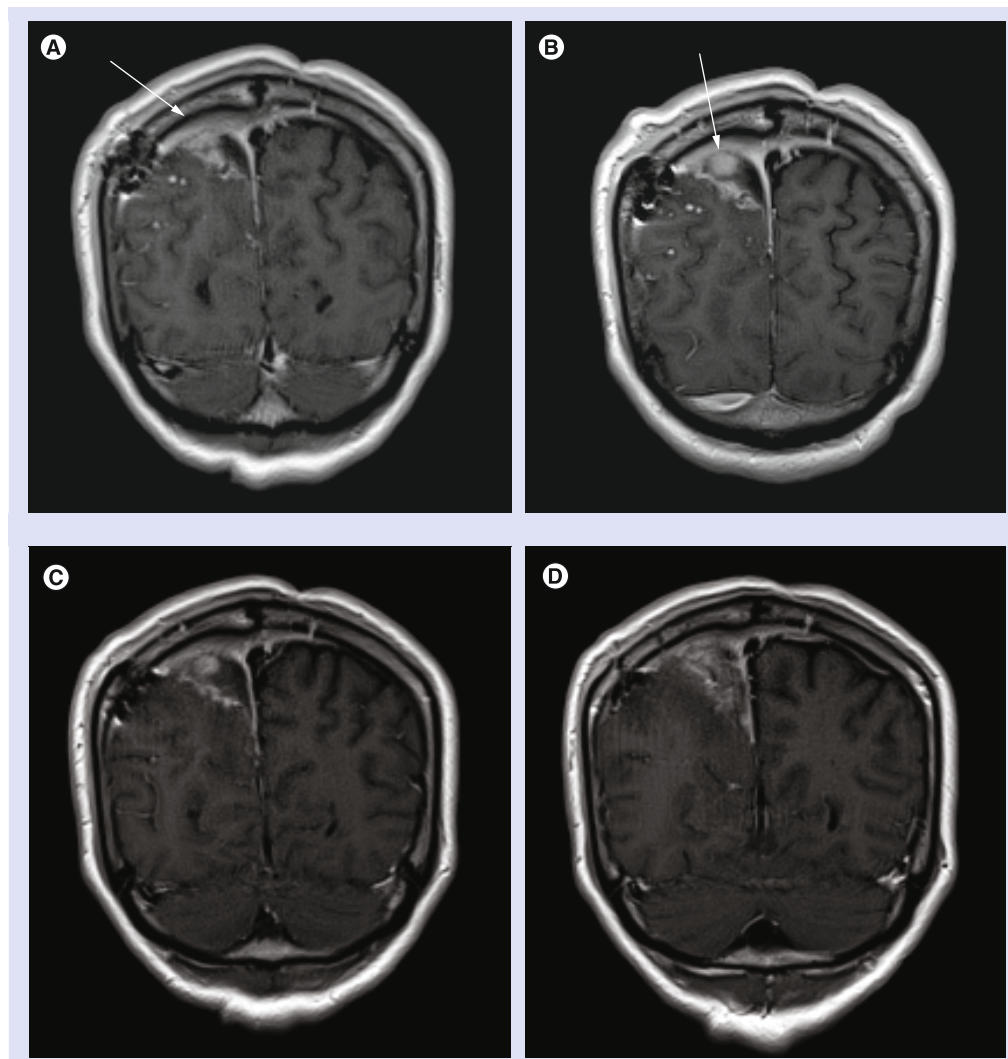
Table 3. Number of patients with renal, hepatic and cardiac impairment by dose in the Phase II–IV studies.

Dose	Special population†		
	Renal impairment	Hepatic impairment	Cardiac impairment
≤0.09 mmol/kg BW	31	9	260
>0.09–0.11 mmol/kg BW	344	127	810
>0.11–0.21 mmol/kg BW	99	22	452
>0.21–0.31 mmol/kg BW	170	49	446
>0.31–0.51 mmol/kg BW	24	7	38
Total	668	214	2006

Patients with missing values are not included in this table.

†Based on information of all 4705 patients administered gadobutrol.

BW: Bodyweight.



**Figure 2. Gadobutrol (A & B) and gadoteridol (C & D) contrast-enhanced spin-echo  $T_1$ -weighted coronal brain images in a patient with brain tumor and postsurgical changes.** Shows dural enhancement (A, arrow) at the right and left frontoparietal lobes, and signs of residual versus recurrence of the tumor with the presence of nodular area of enhancement (B, arrow). (A & B) Show a better degree of enhancement and internal morphology compared with (C & D), while the border delineation of the lesion is similar in enhancement for both contrast agents.

of the given dose is eliminated via the urine. Only a small amount (2.9%) of the dose was excreted after 12 h. Gadolinium concentrations were measurable in urine up to 72 h following administration (TABLE 1) [13].

Fecal excretion was only measured in one study and varied between 0.03 and 0.06% (standard deviation 0.02–0.04) of the injected dose [12].

As with other strongly extracellular GBCAs, there are no ethnic differences in the pharmacokinetics of gadobutrol across Caucasian, Japanese, black or Hispanic populations. The pharmacokinetics of gadobutrol in a pediatric population aged 2 to 17 years old is similar to those in adults [14]. Age has a moderate effect on

the pharmacokinetics of gadobutrol in plasma, showing a reduced plasma clearance, leading to an increase in systemic exposure and to the half-life. Gender has no effect on the pharmacokinetics of gadobutrol, except in elderly women, where a slightly higher area under the plasma concentration versus time curve (area under curve) and a lower clearance may be observed.

No formal drug–drug interaction studies have been performed with gadobutrol and thus the potential is unknown. It is known that gadobutrol has no effect on zinc or iron metabolism. Since gadobutrol is not metabolized, a metabolic drug interaction with a coadministered drug is unlikely.



### Clinical efficacy

Gadobutrol was developed worldwide, for different indications. Globally, gadobutrol has been administered to 313 subjects in Phase I studies and to 4705 patients in Phase II–IV studies including 138 pediatric patients from 2 to 17 years of age (Phase I/III study). Data for pediatric patients are presented in the sections of Phase II–IV. All studies were performed under Good Clinical Practice. Early clinical development in Europe and in Japan focused on a broad range of indications, especially those indications for which other extracellular agents are currently approved.

#### ■ Phase I

In nine Phase I studies, a total of 313 subjects received 0.5 M gadobutrol or 1.0 M gadobutrol

at doses between  $\leq 0.11$  and  $>1.51$  mmol/kg bodyweight (BW).

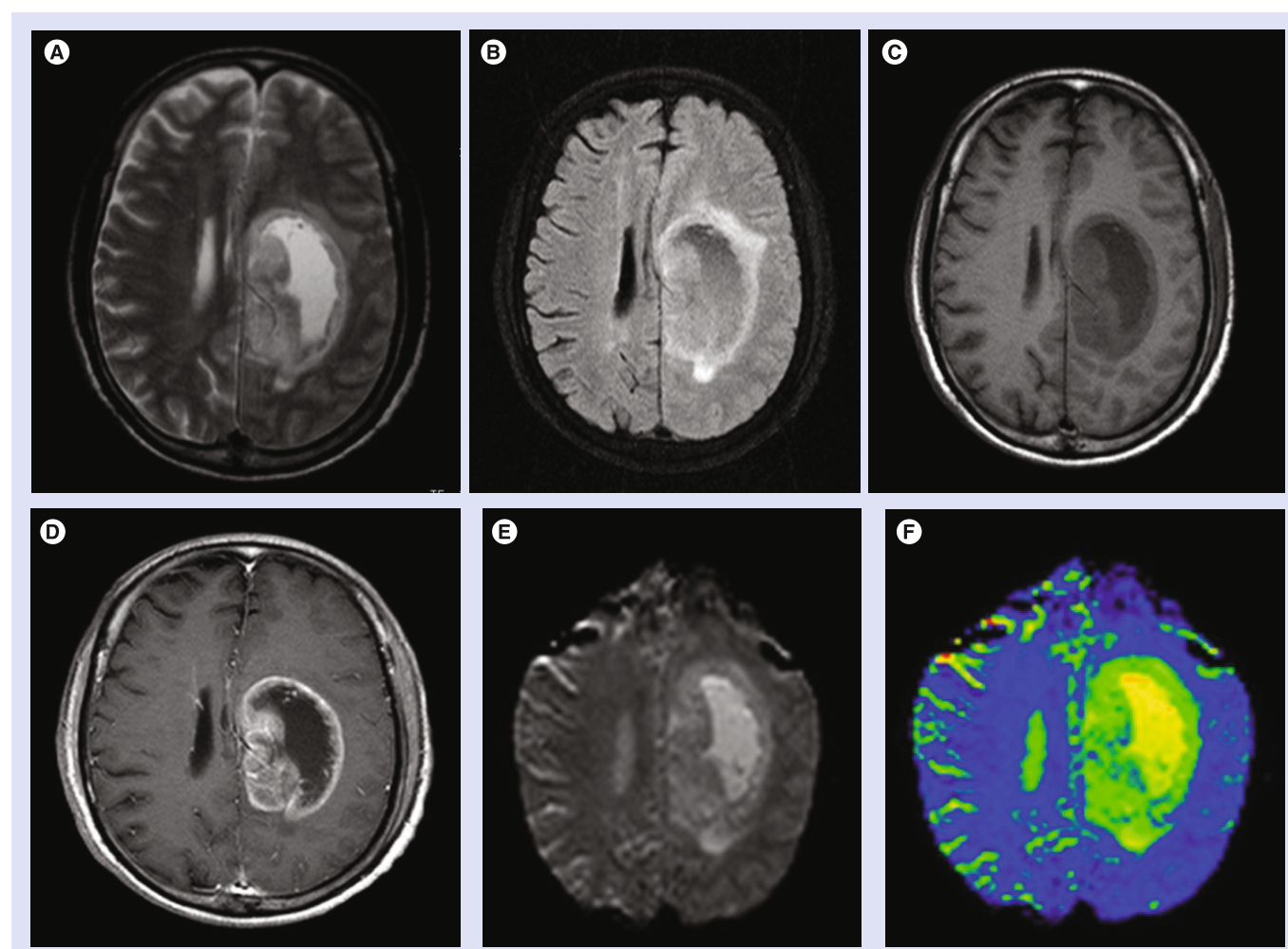
The trials originated in Europe ( $n = 196$ ), Japan ( $n = 56$ ) and the USA ( $n = 61$ ).

#### ■ Phase II–IV

In 35 Phase II–IV studies, gadobutrol has been administered to 4705 patients overall, including 138 pediatric patients.

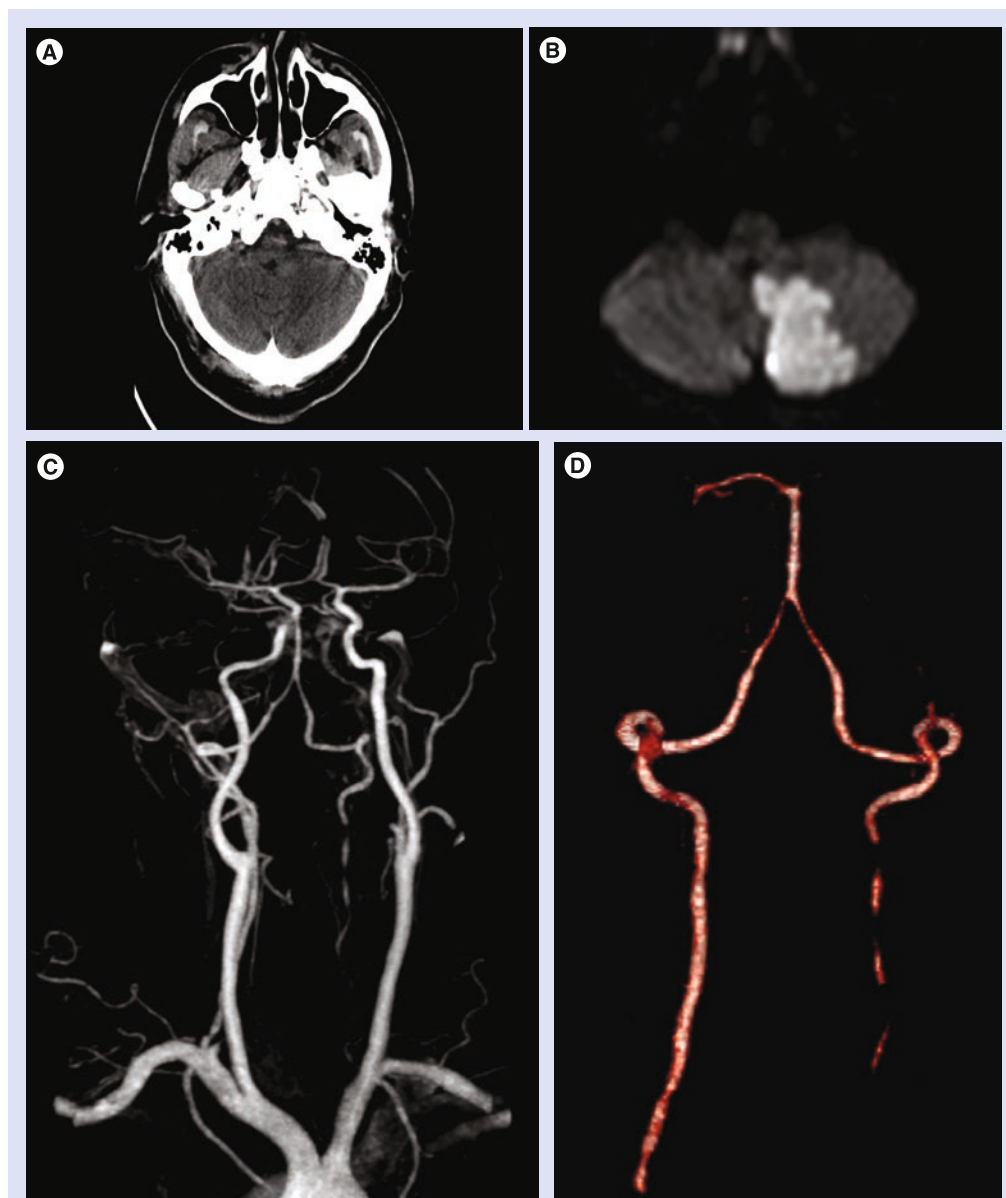
The trials were performed in the EU ( $n = 2901$ ), Asia ( $n = 1223$ ), South/Central America ( $n = 308$ ), USA/Canada ( $n = 264$ ) and Australia ( $n = 9$ ).

A total of 1002 patients received gadobutrol in the concentration of 0.5 M and 3703 patients in the concentration of 1.0 M, with a minimum dose applied of 0.01 mmol/kg BW, and a maximum dose of 0.5 mmol/kg BW.



**Figure 3. Unenhanced spin-echo  $T_1$ -weighted,  $T_2$ -weighted and fluid-attenuated inversion recovery axial brain images.**

Shows a large left parasagittal intra-axial primary brain tumor (glioblastoma multiforme), with mixed intensity on  $T_2$ -dependent sequences (**A & B**) and mainly hypointense in  $T_1$ -weighted image, associated to internal necrosis and vasogenic edema (**C**). Gadobutrol-enhanced  $T_1$ -weighted axial image showing marked enhancement of the solid portion of the lesion as well as its entire border with clear delineation (**D**). Perfusion images (gradient echo–echo planar imaged and colored relative cerebral blood volume map) that correlate accordingly with the primary brain tumor and areas of early necrosis with mixed perfusion (**E & F**).



**Figure 4. Stroke.** Emergency head CT taken 6 h after stroke-like symptoms showing mild hypointensity in the mesial part of left cerebellar lobe **(A)**. Diffusion-weighted brain MR axial scan showing an acute cerebellar ischemic infarct, in the left posterior inferior cerebellar artery vascular territory **(B)**. 1.0 M gadobutrol-enhanced coronal carotid MR angiography and maximum intensity projection showing the subsequent stenosis of the left vertebral artery, however, vertebral hypoplasia cannot be ruled out in this example **(C & D)**.

For the distribution of patients by indication, see TABLE 2.

### Special populations

Three patient subgroups were identified: patients with impaired renal function, patients with impaired hepatic function and patients with impaired cardiac function. The percentages are related to the respective total number of patients ( $n = 4705$ ) who received any dose of gadobutrol. Some studies did not include laboratory measurements.

A total of 668 of 4705 (14.2%) patients of the safety population had any degree of renal impairment with an estimated glomerular filtration rate of less than 90 ml/min.

A total of 214 patients were included with hepatic impairment defined as maximum (AST or ALT) over more than the upper limit of normal value (ULN) or between 1.8 ULN and less than maximum (ALT or AST), less than or equal to 3.0 ULN.

There were 2006 (42.6%) patients with cardiac impairment.

TABLE 3 shows the number of patients with renal, hepatic, and cardiac impairment by dose. There were no clinically significant safety effects revealed during exposure of gadobutrol in the special populations.

### Ongoing Phase III studies

Further developmental activities are currently ongoing for gadobutrol. Two studies with identical study design will evaluate the efficacy and safety of gadobutrol for enhanced breast MRI.

A further study is being conducted in the Asia-Pacific region evaluating the value of gadobutrol in MRI for different body regions (e.g., breast, heart, abdomen, kidney, pelvis or extremities).

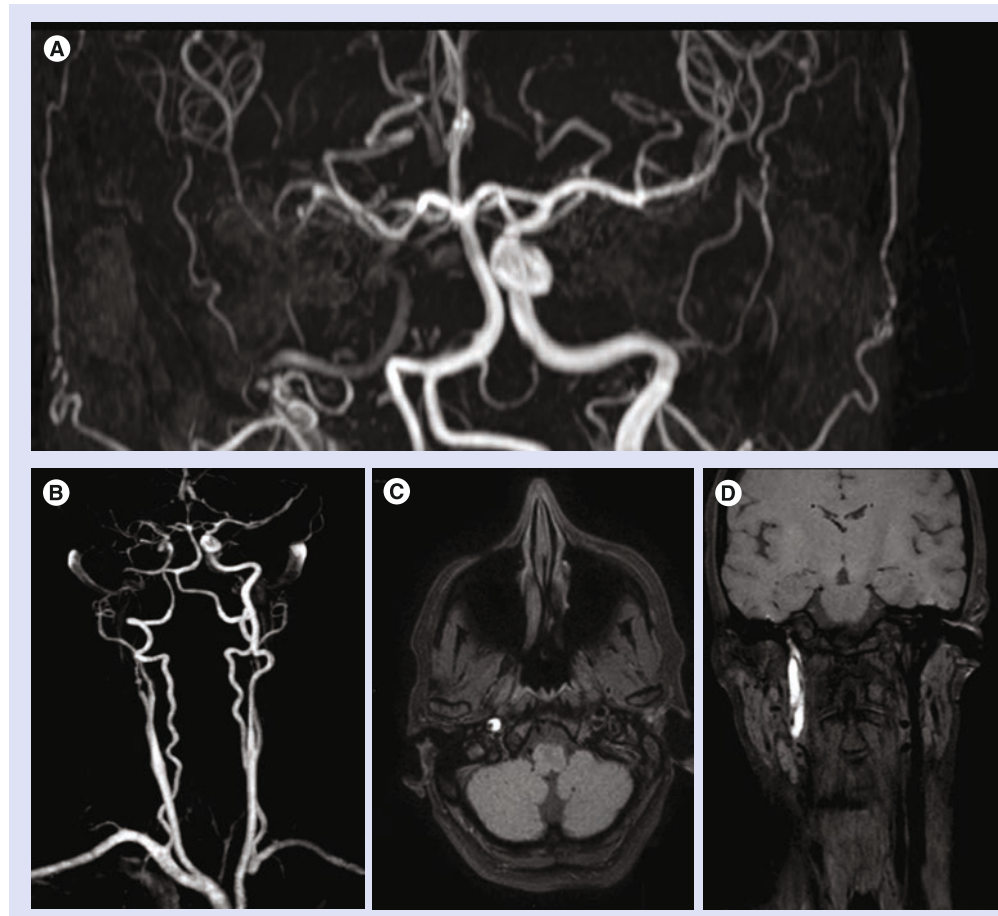
Two studies are planned in the field of contrast-enhanced MRA in renal arteries and supra-aortic arteries for the USA. More detailed information can be found at [101].

### Clinical indications

#### ■ CNS indication

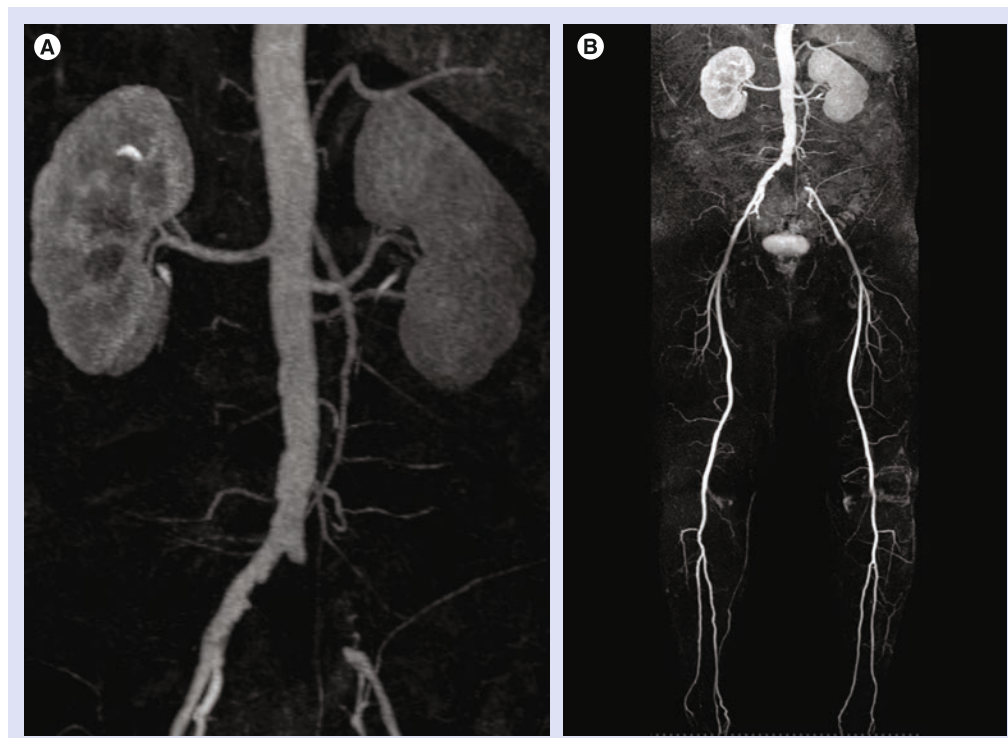
In all trials with CNS indication the common objectives regarding efficacy were to demonstrate an adequate signal increase in diseased areas of brain and spine on  $T_1$ -weighted MRI images, assessment of visualization parameters like border delineation, contrast enhancement, lesion size, internal morphology and adequate signal loss in perfusion imaging of  $T_2^*$ -weighted sequences after intravenous injection of gadobutrol. The majority of trials used the unenhanced (no contrast medium) scans and also an approved extracellular MR contrast agent as the comparator (FIGURES 2 & 3).

Regardless of the gadobutrol concentration, brain and spine lesions were enhanced in the majority of patients on  $T_1$ -weighted images after administration of the contrast media. In perfusion studies at different doses and using  $T_2^*$  fast gradient echo sequences, a signal loss



**Figure 5. 1.0 M gadobutrol-enhanced angiography of extracranial and intracranial carotid artery. (A & B)** 3D TOF (coronal) showing reduction (absence of flow signal) in the right intracranial internal carotid artery; the opposite side a supplementation of right hemispheric circulation is shown. **(C & D)** Spectral presaturation with inversion recovery T-weighted fat-saturated images of the posterior fossa and neck (axial and coronal views, respectively) showing the eccentric semilunar hyperintense signal derived from fresh thrombus or metaHb in the false lumen.





**Figure 6. 1.0 M gadobutrol-enhanced aortoiliac imaging.** 1.0 M gadobutrol-enhanced aortoiliac and lower extremities MR angiography with maximum intensity projection reconstruction  $T_1$ -gradient echo sequence (**A & B**) showing large segment with a lack of lumen enhancement most likely related to occlusion of the left common iliac artery.

was observed, as expected, demonstrating a clear dose dependency, and with echo-planar image sequences, it was shown that the dose can be reduced to 0.1 mmol/kg. Based on prior publications, the possible advantage in perfusion imaging is the better bolus characteristics and high relaxivity as well as the higher concentration of gadolinium in the lesion or region of interest. This has been postulated to open the way for improved diagnostic efficacy not only for the brain but also for CE-MRA [15]. Following the same line of publications, in other comparison studies, it was concluded that the higher concentration 1.0 M gadobutrol can offer advantages over standard 0.5 M gadopentetate dimeglumine, particularly with respect to delineation between gray and white matter and for the demarcation of highly vascularized tumor tissue on brain PWI performed at 3 T [16].

A dose-related improvement for all parameters evaluated could be shown after administration of gadobutrol compared with the unenhanced scans in all studies performed on conventional  $T_1$ -weighted imaging. With regard to lesion detection and visualization of the lesion (border delineation, contrast enhancement, internal morphology and lesion size evaluated in some studies), the dose of 0.1 mmol/kg proved efficacious

in the majority of the subjects, including patients with brain metastases. In comparison to approved extracellular MR contrast agents, the visualization of lesions was proven to be noninferior.

Sensitivity, specificity and accuracy in determining malignant lesions, as evaluated in some studies, increased from unenhanced MRI compared with combined (unenhanced plus gadobutrol enhanced) MRI [17,18].

Based on a majority assessment of blinded readers, sensitivity increased significantly from 51.3 to 71.2%, accuracy increased significantly from 81.7 to 87.5% and specificity increased slightly from 93.7 to 94.0%.

#### ■ Diagnostic confidence

Diagnostic confidence was assessed in some studies, and showed that after an initial dose of 0.1 mmol/kg gadobutrol, there was an increase in confidence by 85 to 90 compared with the unenhanced MRI.

An assessment of the degree of improvement in diagnostic confidence was measured in two studies, with a rating of 'excellent' or 'good' given to 61 and 43% of patients, respectively, with no difference between gadobutrol and gadodiamide [18].



Overall, 1.0 M gadobutrol for CNS imaging is advantageous due to its tight bolus administration and high relaxivity. Gadobutrol 1.0 M has been shown to be noninferior to other approved contrast agents for CNS imaging and has been found by some to have a higher sensitivity and accuracy as well as noninferior diagnostic confidence.

#### ■ CE-MRA indication

In MRA studies, the primary objective was to show diagnostic agreement between gadobutrol-enhanced MRA and intra-arterial digital subtraction angiography (IADSA) for clinically relevant diagnostic patient groups and for prospectively defined vessel segments. Among the studies, vessel segments evaluated were the aortic arch, common carotid arteries, vertebral arteries, subclavian arteries, common or external iliac artery, femoral artery, abdominal aorta, mesenteric arteries, renal artery and peripheral arteries (FIGURES 4 & 5). In one study, the results showed that gadobutrol-enhanced MRA gave comparable results to IADSA for the larger arteries of the pelvis and thigh [19], and another study showed that 1.0 M gadobutrol-enhanced MRA provided an excellent diagnosis or exclusion of pathology

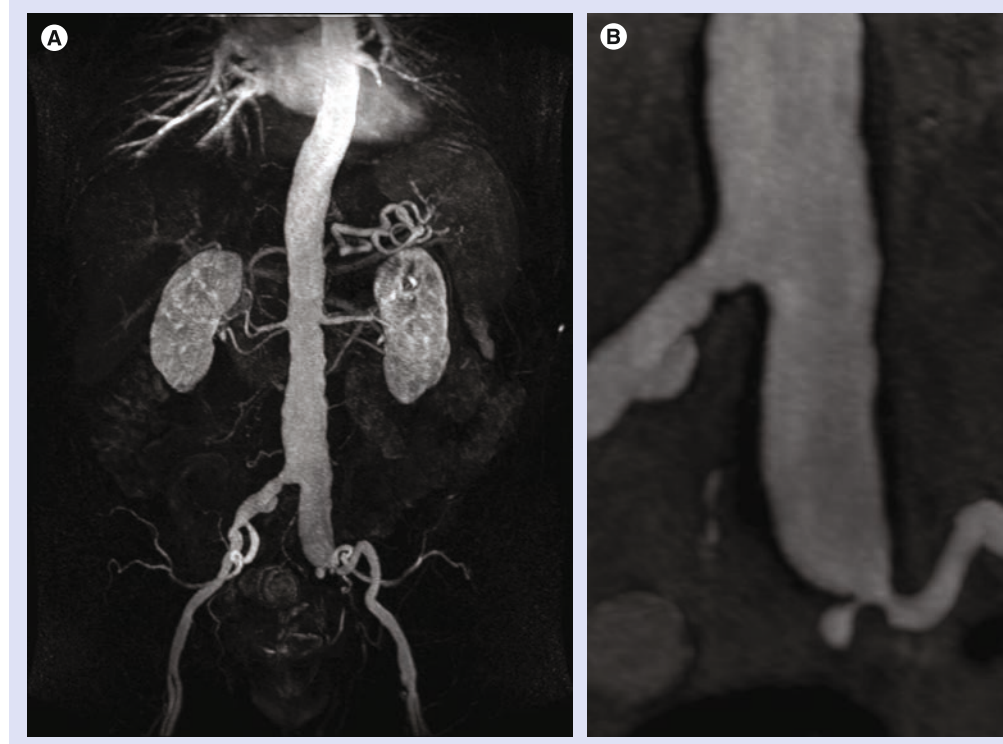
in the aortoiliac vessels [20,21]. Additionally, it was found that contrast-enhanced MRA has very similar outcomes to IADSA for detecting stenosis of the left and right internal carotid arteries and external and common iliac arteries [22], and it has also been shown to be efficacious in imaging of the arteries supplying the spinal cord [23]. Pulmonary studies have indicated that in gadobutrol 1.0 M enhanced-MRA, there was a higher signal-to-noise ratio and contrast-to-noise ratio with noninferior image quality when compared with 0.5 M gadopentetate dimeglumine [24].

In other clinical studies it has been shown that gadobutrol is noninferior to MAGNEVIST for CE-MRA.

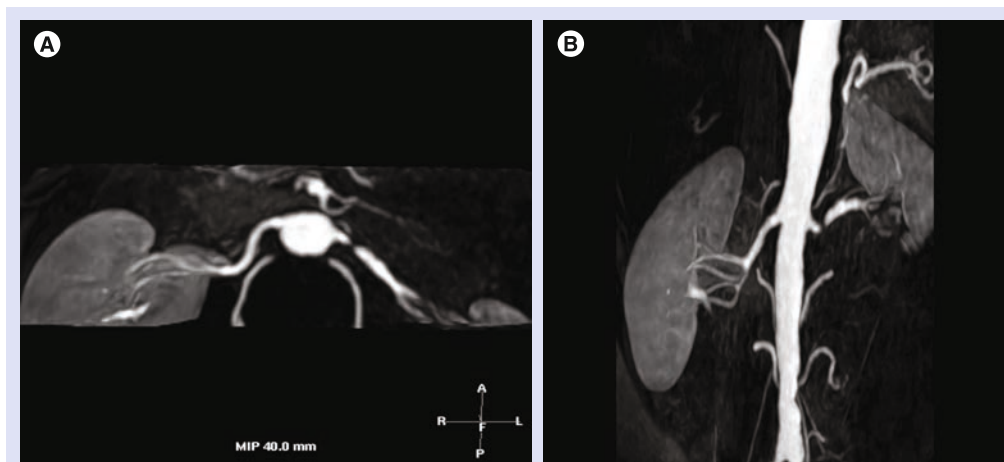
Overall, gadobutrol-enhanced MRA has been found to be equally as efficacious as IADSA and MAGNEVIST-enhanced MRA for imaging large to medium-sized vessel segments (FIGURES 6–8).

#### ■ CE-MRI of other body regions: liver & kidneys

In several studies for visceral applications of gadobutrol, the primary efficacy variables for gadobutrol at a dose of 0.1 mmol/kg BW proved



**Figure 7. 1.0 M gadobutrol-enhanced abdominal aortic imaging.** 1.0 M gadobutrol contrast-enhanced aortoiliac MR angiography with maximum intensity projection reconstruction  $T_1$ -gradient echo sequence and multiplanar reconstruction  $T_1$ -gradient echo sequence (**A & B**) showing aneurysm of the right common iliac artery and aneurysm of the abdominal aorta with small aneurysm sac of the common iliac artery.



**Figure 8. Renal artery stenosis.** 1.0 M gadobutrol-enhanced MR angiography of the renal arteries, axial and coronal maximum intensity projection reconstruction views (**A & B**), showing stenosis of the left renal artery at its origin.

an increase in diagnostic accuracy from pre- to combined pre- and post-contrast MRI scans, thereby a noninferiority to MAGNEVIST was elucidated. Efficacy was determined by clinical investigators and blinded readers. The standard of reference for each study was assessment by an independent truth panel or against a predefined and independent standard of truth. The results showed that the performance of gadobutrol is comparable to MAGNEVIST for both studies and noninferiority was proven for kidney and liver studies [25,26]. Another study indicated that 1.0 M gadobutrol-enhanced MRI of the upper abdominal organs, especially the spleen, pancreas, and kidney, is better due to the higher gadolinium concentration of gadobutrol than in gadoxetic acid [9,27]. In summary, 1.0 M gadobutrol has been shown to be an efficacious agent for imaging of the liver, kidneys, and upper abdominal organs (FIGURES 9–11).

#### ■ Efficacy data for pediatric population

In pediatric patients (aged 2–17 years old) scheduled for CE-MRI of CNS, liver and kidneys or CE-MRA diagnostic efficacy evaluated by means of contrast quality, number of lesions, border delineation, internal morphology and MRI diagnosis, an increase in diagnostic confidence was demonstrated for all parameters evaluated in the study and there was no difference among the age groups.

#### Safety & tolerability

##### ■ Postmarketing surveillance

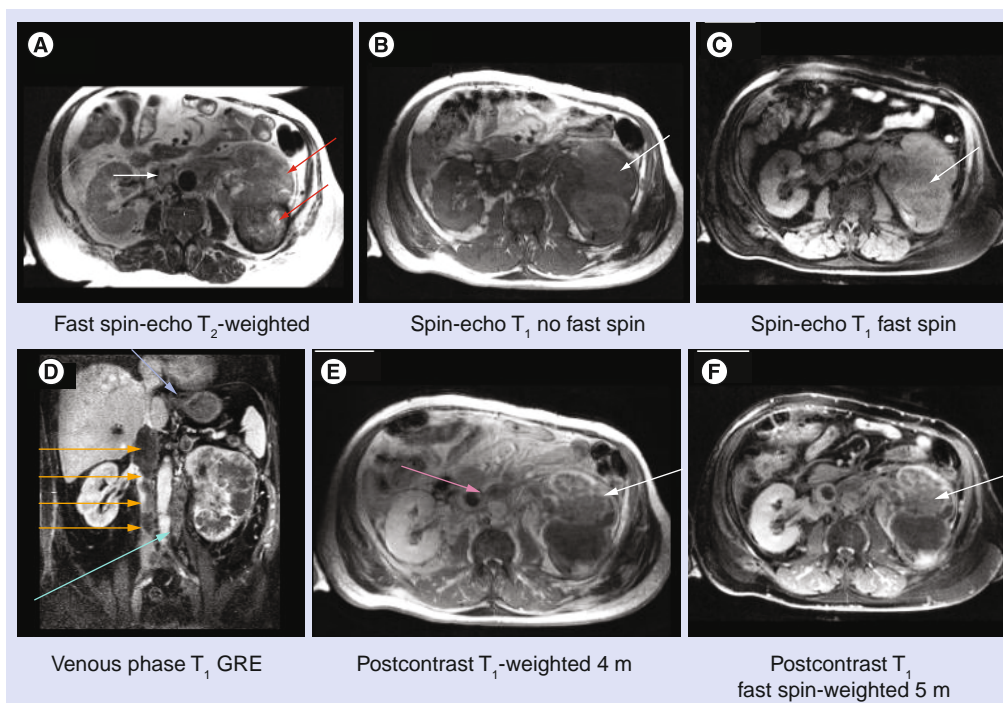
Gadobutrol is approved in 73 countries and has been marketed in 63 countries worldwide as of February 2011. According to the accumulated

global sales and marketing data, it is estimated that Gadovist was administered to approximately 6.8 million patients between its introduction to the Swiss market in 1999 and February 2011. This number includes approximately 180,000 pediatric patients. During the worldwide postmarketing use, there was a total of 1343 suspected adverse drug reactions reported involving gadobutrol. Of those, 942 cases were classified as nonserious and 401 cases were classified as serious case reports. The most serious adverse reactions reported with gadobutrol were cardiac arrest, respiratory arrest, anaphylactoid shock and nephrogenic systemic fibrosis (NSF)-like symptoms. Other individual events were loss of consciousness, convulsion, conjunctivitis, eyelid edema, tachycardia, circulatory collapse, flushing, bronchospasm, cyanosis, oropharyngeal swelling, cough, sneezing, face edema, hyperhidrosis, pruritus, erythema, feeling hot and malaise, which occurred rarely. No episodes of prolonged QT/QTc, malignant arrhythmias or torsades de pointes have been reported. Also, no reports of adverse events have been received in connection with inadvertent double dosing.

Six prospective observation studies were conducted during the period from 2000 to 2007 [11]. In these studies, gadobutrol was administered to a total of 14,299 patients. Examination of the brain and, head and neck was most frequent (54.4%), followed by vessels/MRA (14.4%) and spinal examinations (7.1%). At least one adverse reaction event was observed in 78 of 14,299 patients (0.55%), and two serious adverse reaction events (anaphylactic symptoms and itching and swelling of throat) requiring hospitalization were reported. None of these AEs exceeded a 1% incidence rate.

The most frequently reported adverse reaction was nausea, which was observed in 36 patients (0.25%). Safety data obtained from postmarketing studies suggest high tolerance for gadobutrol, and the safety profile of gadobutrol is consistent with the published data of other extracellular GBCAs including MAGNEVIST. The postmarketing data show that the incidence of adverse reactions is low and with events recognized as adverse drug reactions of Gd-containing contrast agents [28]. The general safety profile was found to correspond well to the data published for other extracellular GBCAs like gadopentetate dimeglumine [102], gadoversetamide [29], gadodiamide [25] or gadoteridol [30].

NSF is a rare, but serious, disease first described in the medical literature in 2000, with the first reported case going back to 1997. NSF has predominantly been reported in patients with severe or end-stage kidney insufficiency or acute kidney injury. Although the precise cause of the disease has not been identified, it is thought to be due to a combination of multiple factors, including the use of GBCAs. One of the prevailing theories as to how GBCAs may be related to NSF is through the dissociation of the gadolinium ion from the underlying chelate. Therefore, based on this theory, the different complex stability of GBCAs may have an impact on the likelihood of triggering NSF [31–35]. Regulators have classified GBCAs (EMA; ACR)



**Figure 9. Fast spin-echo T<sub>2</sub>-weighted, spin-echo T<sub>1</sub> no fast, spin-echo T<sub>1</sub> fast spin, venous phase T<sub>1</sub> gradient echo, postcontrast T<sub>1</sub>-weighted 4 m and postcontrast T<sub>1</sub> fast spin-weighted 5 m.** Unenhanced and gadobutrol contrast-enhanced sequences shows heterogeneous increased signals within the tumor mass of the left kidney and mixed hyperintense/hypointense (A, red arrows) aspects of the tumor. Tumor size is approximately 13 × 9 cm. Inhomogeneous/hyperintense signals are shown in inferior vena cava (A, white arrow). Spin-echo T<sub>1</sub>-weighted image no fast spin shows an inhomogeneous tumor situated in the left kidney (B, white arrow). T<sub>1</sub>-weighted spin-echo image with fast spin shows mixed intensity of left renal mass (C, white arrow). After gadobutrol administration the venous phase in the coronal dynamic series (T<sub>1</sub> GRE 2D with fast spin) shows partly missing contrast enhancement in the inferior vena cava due to tumor invasion over a length of 9 cm (D, orange arrows). Massive invasion into the vena cava up to the liver and downwards expansion until the pelvic inlet. Dilation of vena spermatica (D, green arrow) and diffuse invasion of ipsilateral adrenal gland (D, blue arrow). Postcontrast T<sub>1</sub>-weighted image without fast spin shows the lesion invading into the left pyelocaliceal system, renal hilum and perirenal fat. Massive invasion is also into the inferior vena cava (E, pink arrow) and fat-saturated, contrast-enhanced image shows prominent contrast enhancement in the lesion of the left kidney (E, white arrow). Necrotic and hemorrhagic components become more significant. The mass has a lobulated and nodular appearance (F, white arrow). All findings in relation with renal cell carcinoma.

GRE: Gradient echo.

Image courtesy of Professor Düber, Mainz, Germany.



based mainly on the NSF reporting frequency. The European Medicines Agency – Committee for Medicinal Products for Human Use (EMA-CHMP) assessment, has grouped marketed GBCAs into three different NSF risk categories depending on their conclusions regarding the potential for different GBCAs to trigger NSF [103]. Applying this approach, macrocyclic compounds, including gadobutrol, have been assigned to the low risk group (EMA). Similarly, the ACR also assigned gadobutrol in the low risk class in their guidelines (ACR).

During the entire reporting period through July 2011, Bayer Healthcare has received ten reports suggesting the development of NSF after a reported administration of gadobutrol, including three already published reports [36,37]. An update on NSF can be found at [104]. Based on all available but sometimes incomplete data, an association of NSF-like symptoms to the reported administration of gadobutrol cannot be excluded in three of the overall ten cases. However, in no case was a definite causal role of gadobutrol determined. None of the patients from any clinical trial administering gadobutrol even at doses higher than 0.1 mmol/kg BW, including 194 patients with impaired renal function, have been reported to have developed NSF [38].

#### ■ Safety & tolerability from clinical trials

After the completion of gadobutrol clinical trials, the drug was found to be well tolerated with a comparable safety profile to other extracellular MR contrast agents. Evaluation of special populations like pediatric patients, renal impairment, hepatic impairment and patients with cardiovascular disorders did not reveal any specific risk in these populations.

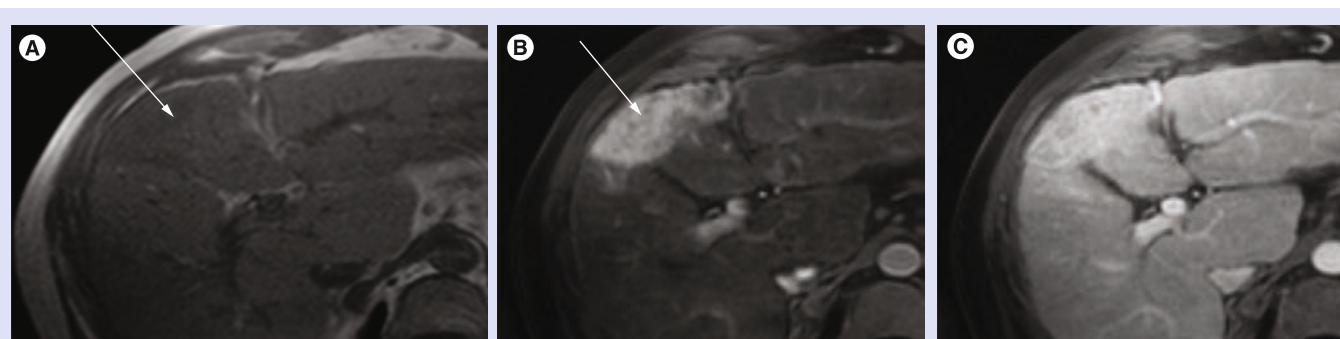
Overall, 4.0% of 4705 subjects reported one or more adverse drug reactions during a follow-up period from 24 h to 7 days after gadobutrol administration. The most frequent ( $\geq 0.5\%$ ) adverse drug reactions associated with the use of gadobutrol are headache, nausea, injection-site reaction, dysgeusia and feeling hot. Adverse reactions following gadobutrol administration are usually mild to moderate in severity and transient in nature. No obvious relationship was noted between the incidence of drug-related adverse events and the dose of gadobutrol (TABLE 4).

Adverse reactions that occurred with a frequency of less than 0.1% in subjects in clinical trials and treated with gadobutrol include: hypersensitivity/anaphylactoid reactions (hypotension, urticaria, flushing, pallor), loss of consciousness, convulsion, parosmia, tachycardia, palpitation, dry mouth, malaise and feeling cold.

From more than 6.8 million administrations after the first launch of gadobutrol in Switzerland in 1999, the following adverse drug reactions have been reported during post-marketing use. As 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.

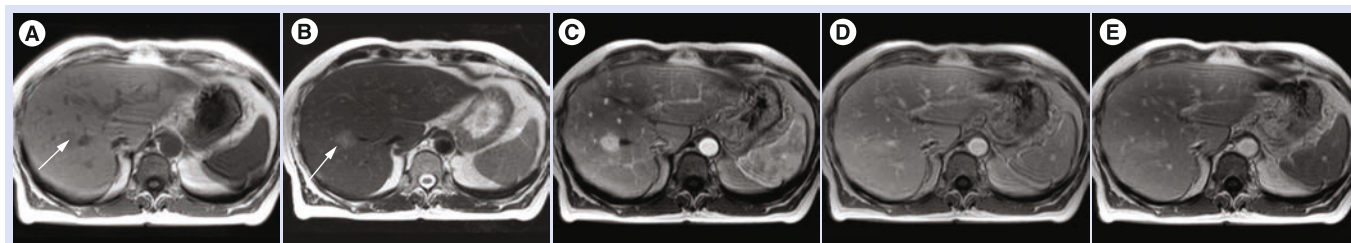
- Cardiac arrest
- NSF

Hypersensitivity/anaphylactoid reactions reported from postmarketing use include the following: anaphylactoid shock, circulatory collapse, blood pressure increase, chest pain, respiratory arrest, bronchospasm, cyanosis, oropharyngeal swelling, laryngeal edema, face edema, angioedema, conjunctivitis, eyelid edema,



**Figure 10. Unenhanced and gadobutrol contrast-enhanced (arterial and venous phases) T<sub>1</sub>-weighted axial sequences (A–C) of the liver, showing irregular mass invading segments 4A and 8. This lesion is irregular and isointense in the unenhanced image and with significant enhancement on the arterial phase shows irregularity of its borders and small areas of necrosis with partial washout of the contrast on the venous phase. All findings in relation with hepatocellular carcinoma.**





**Figure 11. Unenhanced T<sub>1</sub>-weighted (A)–T<sub>2</sub>-weighted (B) and gadobutrol contrast-enhanced (arterial, venous and equilibrium phases) T<sub>1</sub>-weighted axial sequences (C–E) of the liver in a patient with metastasis of a known primary tumor.** Showing a single round lesion in segment 5/6, this lesion is regular hypointense and hyperintense in the unenhanced T<sub>1</sub>-weighted and T<sub>2</sub>-weighted images, respectively. Bright complete enhancement on the arterial phase, showing partial washout of the contrast on the venous and equilibrium phases.

hyperhidrosis, cough, sneezing and burning sensation.

To minimize the risk of NSF, health authorities worldwide have implemented respective warnings for the use of GBCAs. This also applies to gadobutrol. The warning describes the risk for this disease in patients receiving these agents and who suffer from renal dysfunction meeting one of the following conditions:

- Chronic, severe kidney disease (GFR <30 ml/min/1.73 m<sup>2</sup>)
- Acute kidney injury
- Acute renal insufficiency of any severity due to hepatorenal syndrome or in the perioperative liver transplantation period.

### Regulatory affairs

Gadobutrol is currently approved for CNS indication in the USA, and for multiple other indications in the rest of the world. So far it is the only macrocyclic, highly concentrated (1.0 M) form of gadolinium available in the market worldwide.

Outside of the USA, 0.5 M and 1.0 M gadobutrol was first approved for CNS indication in Switzerland in 1998. Whereas in the EU, Australia and Canada approval took place between 1999 and 2000.

Discontinuation of development and marketing for the 0.5 M formulation occurred in 1997.

Approval for MRA indication 1.0 M Gadobutrol occurred in the EU during 2003.

Gadobutrol 1.0 M received EU approval for body indications during 2007.

Approval for pediatric use aged 2 years and above in Switzerland, Canada, China, Korea and aged 7 years and above in EU 2010.

In the USA regulatory overview includes:

- Original investigational new drug, July 1988, then inactivated in 1999
- Investigational new drug reactivated in 2004
- US FDA approval for CNS in adults and pediatric patients 2 years and above 2011

### Conclusion

It is well known that combined MRI with and without GBCA is the one of the best

**Table 4. Adverse reactions.**

Reaction	Rate (%), n = 4705
Headache	1.5
Nausea	1.2
Injection-site reaction (various kinds) <sup>†</sup>	0.6
Dysgeusia	0.5
Feeling hot	0.5
Dizziness	0.4
Vomiting	0.4
Rash (includes generalized, macular, papular, pruritic rash)	0.3
Pruritus (includes generalized pruritus)	0.1
Erythema	0.1
Dyspnea	0.2
Paresthesia	0.1

<sup>†</sup>Includes injection-site extravasation, injection-site burning, injection-site coldness, injection-site warmth, injection-site erythema or rash, injection-site pain and injection-site hematoma (adverse events coded by MedDRA, [v 12.1]).

imaging methods to define normal anatomy and characteristics of lesions (location, size, number, border delineation, degree of edema, contrast enhancement). Gadobutrol is a macrocyclic nonionic, extracellular gadolinium-based contrast agent with high paramagnetic effect (relaxivity). Its concentration is higher compared with other similar approved products (1.0 vs 0.5 M). Studies have shown that gadobutrol provides higher image quality in body, CNS and MRA contrast imaging. Its high concentration may have potential advantages, especially for fast dynamic images, which may need to be elaborated in further clinical studies.

Gadobutrol should be administered for MR contrast enhancement at a dose of 0.1 mmol/kg (0.1 ml/kg). It is as safe and effective as other approved gadolinium-based contrast agents based on the results of the different clinical trials worldwide. Furthermore, with the known NSF risk related to GBCAs, it is important to know that macrocyclic molecules have a high kinetic and thermodynamic stability.

### Future perspective

1.0 M gadobutrol, the first GBCA approved for use at a concentration of greater than 0.5 M, it has the potential to increase the robustness of CE-MRI of all types by providing better visibility of tissues with its high relaxivity. Since it was first approved in 1998, gadobutrol has continually demonstrated its broad range of applications, which are continually expanding and advancing the diagnostic and clinical application of CE-MRI and MRA.

### Financial & competing interests disclosure

*J Breuer is a Bayer HealthCare employee, JE Gutierrez is a research consultant at Bayer HealthCare Gadovist Speaker Bureau. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

*No writing assistance was utilized in the production of this manuscript.*

## Executive summary

### Mechanisms of action

- Gadobutrol 1.0 M is a nonionic macrocyclic extracellular MRI contrast agent with high stability and relaxivity.
- It is injected as a tight intravenous bolus at 1.0 M concentration and improves the relaxivity of tissues throughout the body for better visualization on MRI by shortening the  $T_1$  and  $T_2$  relaxation times.

### Pharmacokinetic & pharmacodynamic properties

- After a single intravenous administration, gadobutrol distributes rapidly into the extracellular space followed by a fast first-order renal elimination of the unchanged drug.
- Gadobutrol improves the detection and visualization of specific features of pathologies/lesions by showing abnormal vascularity and remaining in the vessels for a short time, leaking through a disrupted blood barrier, or being distributed into the extracellular space.

### Clinical efficacy

- Gadobutrol has been shown to be efficacious for CNS imaging by improving visualization parameters, such as border delineation, contrast enhancement, lesion size and internal morphology.
- Gadobutrol has been shown to give comparable results in MRA of large- and medium-sized arteries to intra-arterial digital subtraction angiography for the detection of stenosis.
- Applications for evaluating pathologies in the liver and kidneys have been shown to be noninferior to studies conducted with MAGNEVIST™.
- Gadobutrol is efficacious in pediatric patients aged from 2 to 17 years old.

### Safety & tolerability

- Safety is comparable to other extracellular MR contrast agents.
- Safety data do not indicate an increased risk in patients with renal impairment, hepatic impairment or cardiovascular disorders, and there are no reports of increased risk to pediatric patients.
- Adverse reactions that occurred with a frequency of approximately 4% in subjects of clinical trials and treated with gadobutrol are generally mild to moderate in severity and include: headache, nausea, injection-site reaction, dysgeusia and feeling hot.
- Hypersensitivity/anaphylactoid reactions are observed in less than or equal to 0.1% of patients and is a rare occurrence.
- As for other gadolinium-based contrast agents warnings have been implemented for the use in chronic severe kidney disease ( $GFR < 30 \text{ ml/min/1.73 m}^2$ ), acute kidney injury or acute renal insufficiency.

### Drug interactions

- No formal drug–drug interaction studies have been performed with gadobutrol and thus the potential is unknown.
- Since gadobutrol is not metabolized, a metabolic drug interaction with a coadministered drug is unlikely.

### Dosage & administration

- Gadobutrol 1.0 M is generally administered as a single intravenous bolus of at a dose of 0.1 mmol/kg bodyweight, and it has been approved for use at doses of up to 0.3 mmol/kg bodyweight in some countries.

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