

Safety of Gadobutrol, a New Generation of Contrast Agents

Experience From Clinical Trials and Postmarketing Surveillance

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Objective: To assess the clinical safety and tolerability of the macrocyclic contrast agent gadobutrol (Gadovist/Gadavist) overall and in specific patient populations based on clinical trials and postmarketing experience.

Materials and Methods: In total, 5545 patients enrolled in 34 prospective clinical studies were evaluated in an integrated analysis of safety. Of all enrolled patients, 4549 received gadobutrol at a dose of ≤ 0.09 mmol/kg body weight to a maximum of 0.51 mmol/kg body weight, with most patients (53.5%) receiving the recommended dose of >0.09 to 0.11 mmol/kg body weight. Data include comparisons with other extracellular contrast agents and subgroup analyses in pediatric patients, and patients with allergic disposition, renal impairment, hepatic impairment, or cardiovascular disease. Furthermore, worldwide postmarketing safety surveillance results, including nephrogenic systemic fibrosis reports, based on more than 5.7 million estimated applications are described.

Results: One or more adverse events (AEs) assessed as related to the administration of gadobutrol were reported by 182 (4.0%) of the 4549 patients who participated in clinical trials. This is comparable to the incidence observed with the comparator contrast agents (74/1844 patients, 4.0%). The most common AEs, independent of drug relationship, were headache, nausea, feeling hot, and dysgeusia. The favorable safety profile of gadobutrol was also demonstrated in the following specific subpopulations in whom similar incidence rates were seen: pediatric patients aged 2 to 17 years (8/138 patients, 5.8%), patients with severe or moderate renal impairment (9/366 patients, 2.5%), patients with severe or moderate hepatic impairment (9/214 patients, 4.2%), and patients with cardiovascular disorders (42/1506 patients, 2.8%). Having been established in controlled clinical trials, this safety profile was also confirmed by postmarketing surveillance data. With more than 5.7 million estimated administrations of gadobutrol, a total of 1175 (0.02%) suspected adverse drug reactions have been reported. The most serious adverse reactions seen in postmarketing surveillance included rare reports of cardiac arrest, respiratory arrest, anaphylactoid shock, and nephrogenic systemic fibrosis. Incidence and type of AEs from postmarketing surveillance were consistent with the established safety profile.

Conclusion: The comprehensive analysis of safety data obtained from 34 clinical studies demonstrates that gadobutrol has an excellent safety profile and a positive benefit risk profile when used in patients in need of contrast-enhanced magnetic resonance imaging. Gadobutrol was well tolerated by adults, by children, by patients with impaired liver or kidney function, and by patients with cardiovascular disease. The favorable safety profile is confirmed by the available postmarketing surveillance data and is compared with that of other gadolinium-based contrast agents.

Key Words: gadolinium/diagnostic use, MR imaging, contrast-enhanced MR, human

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Magnetic resonance (MR) imaging is routinely used in several clinical pathways where it is pivotal for accurate disease detection, disease characterization, and treatment planning. An increasing number of MR imaging examinations require the intravenous administration of gadolinium-based contrast agents (GBCAs). These agents contain a central gadolinium ion (Gd^{3+}), which exhibits paramagnetic properties that lead to contrast enhancement by shortening of the T1 and T2 relaxation times.^{1,2} As the free Gd ion itself has demonstrated toxicities at sufficient concentrations, all GBCAs possess ligands that effectively bind the Gd ion by chelation.

Gadobutrol (Gadovist/Gadavist) is a nonionic, macrocyclic Gd-chelate of low osmolality and low viscosity. Gadobutrol belongs to the class of macrocyclic extracellular GBCAs, considered the least prone to Gd dissociation and/or to transmetallation.³ Currently, it is indicated for use in central nervous system imaging, magnetic resonance angiography, as well as liver and kidney imaging (the approved indications differ by country). The generally recommended dose for injection is 0.1 mmol gadobutrol per kg body weight, administered as an intravenous bolus injection often using a power injector at a flow rate of approximately 2.0 mL/s. Doses up to 0.3 mmol/kg body weight are approved in several regions worldwide. Following intravenous injection, gadobutrol rapidly passes to the extracellular space and is quickly eliminated by glomerular filtration. Gadobutrol filtered from glomeruli is excreted in urine without any change. Metabolites are neither detected in plasma nor in urine.⁴ Because of renal elimination, consideration of safety aspects in renally impaired patients is of particular importance.

The marketed formulation of gadobutrol is available at a concentration of 1.0 M (1.0 mmol/mL), combining the high relaxivity (high paramagnetic effect) with a more compact bolus profile, resulting in a pronounced T1 shortening. The improved performance for diagnostic procedures compared with other GBCAs of 0.5 M concentration is described in numerous publications.^{5–12}

Gadobutrol, first approved in Switzerland in 1998, is currently (March 2011) approved in 66 countries including all of the European Union countries, United States, Australia, Canada, China, South Africa, Mexico, New Zealand, Turkey, and several Eastern European and Asian countries.

Previously, Balzer et al¹³ summarized the safety of gadobutrol in 435 patients enrolled in 3 multicenter trials who had an indication for contrast-enhanced (CE) MR angiography of supra-aortic, abdominopelvic, or peripheral arteries. Palkowitsch and Voth¹⁴ summarized the safety experience of more than 2900 patients recruited in clinical trials mainly for CE-MR imaging of the central nervous system (CNS), liver, kidney, and CE-MR angiography.

To critically evaluate the clinical safety of gadobutrol, we performed an updated integrated analysis of 34 clinical trials. For comparison, safety data of other broadly used GBCAs are included.

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Particular emphasis was put on the analysis of patients with renal, hepatic, or cardiovascular impairment, patients presenting with allergies, and safety in pediatric use. Results of the integrated analysis are presented together with results of individual trials designed to evaluate safety in special populations. Furthermore, we reviewed postmarketing surveillance data obtained since the market introduction of gadobutrol.

MATERIALS AND METHODS

Patients and Contrast Agents

The integrated, retrospective analysis encompasses a total of 5545 patients enrolled in 34 clinical trials who received either only gadobutrol and/or a comparator contrast agent. All trials were prospectively planned and were conducted between 1993 and 2009 in compliance with "International Conference on Harmonization Good Clinical Practice" guidelines following approval by applicable ethics committees/institutional review boards (<http://clinicaltrials.gov>). Prior to the start of the study, written informed consent was obtained from each patient.

In 20 studies, patients received a single gadobutrol treatment. Controlled trials included 9 parallel-group design studies and 5 crossover studies in which patients received either different gadobutrol doses or gadobutrol and a comparator contrast agent. The total number of patients (6393) analyzed was higher than the number of enrolled patients (5545) as because of the crossover design some patients from 4 clinical trials were analyzed by period and counted twice when they, after a wash-out period of at least 24 hours, continued in the second period with another study drug.

In total, 4549 patients were treated with gadobutrol. Gadobutrol was administered in doses ranging from less than 0.09 to 0.51 mmol/kg body weight; the majority (2434 patients, 53.5%) received the generally recommended dose of 0.1 (± 0.01) mmol/kg body weight. In other indications such as peripheral magnetic resonance angiography, brain perfusion, and cardiac perfusion, higher doses of gadobutrol were also studied.

A total of 1844 patients were treated with a comparator contrast agent, that is, gadopentetate dimeglumine (Magnevist, BayerHealthCare, Berlin, Germany, $n = 912$ patients), gadoteridol (ProHance, Bracco SpA, Milan, Italy, $n = 555$ patients), gadoversetamide (OptiMark, Covidien, Hazelwood, MO, $n = 227$ patients), or gadodiamide (Omniscan, GE Healthcare, Little Chalfont, UK, $n = 150$ patients). The majority (86.8%) of the patients received the comparators at a dose of 0.1 mmol/kg body weight. In 13.2% of the patients (8.8% gadoteridol, 4.4% gadopentetate dimeglumine), the comparator contrast agents were used with a double dose of 0.2 mmol/kg body weight.

Safety Monitoring

Safety monitoring, defined in detail in each study, generally encompassed continuous adverse events (AEs) monitoring, comparison of laboratory parameters determined prior to the injection of the contrast agent with those recorded after injection, vital signs (systolic and diastolic blood pressure values, and, in some studies, respiration rate, body temperature), physical examination, and electrocardiogram (ECG, performed in 9 of the 34 studies) during a follow-up period from 24 hours to 7 days after contrast administration.

AEs (treatment emergent signs and symptoms) were coded using MedDRA version 12.1. In the integrated, retrospective analysis, AEs were considered to be treatment-emergent if they started between start of the injection and up to 72 hours after the injection (all studies), or in crossover studies, at the beginning of the next period, whichever occurred first. Each AE was assigned to the treatment group/period in which it appeared. Intensity (mild, moderate, severe) and relationship of the AE to the study drug (related

or unrelated) were assessed by the clinical investigators. An overall assessment of adverse drug reactions is given according to the definition of the FDA guidance¹⁵ (ie, adverse drug reactions are those AEs for which there was some basis to believe there may be a causal relationship between the drug and the occurrence of the AE) using a conservative approach: As soon as a possible causal relationship between an AE (by MedDRA preferred term) and a contrast agent was assessed by the sponsor and/or one of the investigators, all AEs of this preferred term were considered a potential adverse drug reaction even if no causal relationship was assessed for all other AEs of this preferred term, leading to higher incidence rates. Serious AEs (SAEs) were those reactions that resulted in death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that might not have been immediately life threatening or resulted in death or hospitalization but might have jeopardized the patient or might have required intervention to prevent one of the other outcomes listed above, and any suspected transmission via a medicinal product of an infectious agent, were also considered SAEs.

Renal Safety Assessment

Renal function was assessed based on the level of the estimated glomerular filtration rate (eGFR) immediately prior to injection, which was categorized in 4 groups: <30 mL/min, $30- <60$ mL/min, $60- <90$ mL/min, and ≥ 90 mL/min. If not given otherwise in the original study, eGFR was computed as follows: Japanese male subjects: $eGFR = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{0.287}$; Japanese female subjects: formula for male Japanese corrected by a factor of 0.739; other adult subjects: according to the Cockcroft-Gault formula¹⁶; pediatric subjects: according to the formula by Schwartz et al, 1987.¹⁷

One of the 34 trials included 23 male and 9 female patients and was specifically designed to study the safety of gadobutrol administered in doses of 0.1 and 0.3 mmol/kg body weight ($n = 16$ patients each) in patients with renal impairment (defined by eGFR <30 mL and ≥ 30 to <80 mL/min, respectively) and in patients on hemodialysis. The primary variable for patients with impaired renal function was the change in creatinine clearance. For patients on dialysis, the primary variable was the decrease of serum gadobutrol with each dialysis session performed post injection.

Hepatic Safety Assessment

Liver function was categorized in 3 groups based on the maximum of baseline values for alanine aminotransferase (ALT) or aspartate aminotransferase (AST): 3.0 upper limit of normal range (ULN) $<$ maximum value for ALT or AST, 1.8 ULN $<$ maximum value for ALT or AST ≤ 3.0 ULN, and maximum value for ALT or AST ≤ 1.8 ULN.

Cardiac Safety Assessment

Patients with abnormal cardiovascular findings were identified based on their medical history and initial physical examination. Patients with severe cardiovascular disorder had at least one of the following concomitant diseases/conditions: (absolute) arrhythmia, angina pectoris, atrial fibrillation, bypass, coronary artery bypass graft, coronary artery disease, coronary disease, coronary heart disease, coronary stent, ischemic coronary attack, or myocardial infarction. Twelve-lead electrocardiogram (ECG) evaluations were performed in 9 of the 34 studies encompassing 1014 patients at baseline and in 6 studies (910 patients) with at least one ECG after injection. The Fridericia formula was used predominantly for QT correction (QTcF). Values and shifts which might be of clinical importance were analyzed.

In addition, a potential influence of gadobutrol on cardiac repolarization was analyzed in a single-center, randomized, placebo-

controlled, 5-period crossover, dose-comparison study with a concurrent positive control in 64 healthy male and female subjects (so called “thorough” QTc study). Each subject was planned to receive all 5 injections in a randomized order, that is, 3 doses of gadobutrol (0.1, 0.3, and 0.5 mmol/kg body weight), placebo (0.9% saline), and positive control (moxifloxacin, 400 mg intravenously), with a 4 to 14 day washout period between the study injections. The design was double-blind for gadobutrol and placebo. Twelve-lead continuous ECG recordings were evaluated offsite by independent cardiologists blinded to the 5 treatments. The primary study end point was the average change from baseline within 15 minutes post contrast in the QTcF interval. QTcF measurements were compared with placebo (0.9% saline solution) as a negative control and with moxifloxacin (400 mg) as a positive control. AEs were monitored throughout the study. AEs that could potentially be related to ECG abnormalities (eg, cardiac arrhythmias, dizziness, palpitations, syncope, and seizures due to cerebral ischemia resulting from arrhythmia, sudden cardiac death, and any serious cardiac AEs) were evaluated separately. Other safety assessments included clinical laboratory tests, vital signs, and physical examination. Any changes of potential clinical importance from pre contrast were evaluated.

Safety Assessment by History of Allergies

Patients with a history of allergies/anaphylactoid reactions, including allergies/anaphylactoid reactions to contrast media (including iodine), were identified based on the recordings in their medical history and physical examination.

Postmarketing Safety Surveillance

A summary of spontaneous reports is provided after more than 5.7 million subjects have received gadobutrol since the approval in 1988.

Special focus was laid on a possible association of gadobutrol administration with development of nephrogenic systemic fibrosis (NSF) like symptoms. Because of the nature of spontaneous reporting, necessary information was not always available and substantial efforts have been taken to fill information gaps, however, not always successfully. While the actual cause of NSF is not entirely understood and considered multifactorial, GBCAs have been considered a relevant factor in the development of NSF.¹⁸ The strength of such a possible association of a reported NSF case with the administration of macrocyclic gadobutrol was assessed using the following criteria (adapted based on Broome et al, 2007)¹⁹: (a) Confirmation of the NSF diagnosis by skin biopsy or based solely on clinical manifestations; (b) Documentation of the use of gadobutrol in contrast administration records; (c) Temporal relationship of contrast administration and development of NSF documented (for this not only the usually used time period of 2 weeks to 3 months, but the significantly longer period of 18 months post contrast administration was taken into consideration); (d) Verification whether the patient may have been exposed to multiple MR contrast agents (again taking a period of 18 months into consideration). To consistently evaluate the cases reported or suspected as NSF, additionally yet unpublished guidelines for a standardized NSF definition established by a working group of experts led by Dr. Shawn Cowper (Cowper S, Kay J, Elston D, LeBoit P, Girardi M. The Clinicopathological Definition of Nephrogenic Systemic Fibrosis, personal correspondence) were taken into account. The NSF score is based on the clinical presentation and on histopathologic results and arrives at 1 of 6 possible diagnosis or conclusions: NSF confirmed, consistent with NSF, suggestive of NSF, inconsistent with NSF, not NSF/NSF ruled out, or alternative diagnosis/diagnostic of an entity other than NSF.

Statistical Analyses

The statistical evaluation was performed using the SAS software release 9.1 (SAS Institute Inc, Cary, NC) for UNIX. All variables were

TABLE 1. Demographic Data of the Patients Receiving Gadobutrol or a Comparator Contrast Agent (N, %)

	Gadobutrol	Comparator*	All Treatments
No. patients	4549 (100.0%)	1844 (100.0%)	6393 (100.0%)
Gender			
Male patients	2663 (58.5%)	971 (52.7%)	3634 (56.8%)
Female patients	1886 (41.5%)	873 (47.3%)	2759 (43.2%)
Ethnic origin			
White	2949 (64.8%)	991 (53.7%)	3940 (61.6%)
Black	58 (1.3%)	42 (2.3%)	100 (1.6%)
Hispanic	135 (3.0%)	44 (2.4%)	179 (2.8%)
Asian	1242 (27.3%)	673 (36.5%)	1915 (30.0%)
Other	165 (3.6%)	94 (5.1%)	259 (4.1%)
Age, yr			
Mean $\pm$ SD	54.2 $\pm$ 16.6	54.7 $\pm$ 14.5	54.3 $\pm$ 16.2
Range	2–93	18–89	2–93
Body weight, kg [†]			
Mean $\pm$ SD	69.5 $\pm$ 17.0	69.6 $\pm$ 16.9	69.5 $\pm$ 17.0
Range	10.7–145.0	30.9–145.0	10.7–145.0
Region			
Europe	2745 (60.3%)	789 (42.8%)	3534 (55.3%)
USA/Canada	264 (5.8%)	194 (10.5%)	458 (7.2%)
South/Central America	308 (6.8%)	184 (10.0%)	492 (7.7%)
Asia	1223 (26.9%)	668 (36.2%)	1891 (29.6%)
Australia	9 (0.2%)	9 (0.5%)	18 (0.3%)

*Contrast agents used were gadopentetate dimeglumine, gadoteridol, gadoversetamide, and gadodiamide.

[†]For 2 patients of the gadobutrol group the body weight was missing.

analyzed by descriptive statistical methods. All analyses were performed post hoc. AE incidence rates were calculated for gadobutrol and the various comparator contrast agents by dividing the number of patients reporting AE by the number of patients exposed.

RESULTS

Demographic Data and Baseline Characteristics of Clinical Trial Patients

Of the 4549 patients exposed to gadobutrol, most (4411 patients, 97%) were adults and 138 were children aged 2 to 17 years recruited in one pediatric study. The average age was 54.2 years

TABLE 2. Incidence of Adverse Events

	Gadobutrol		Comparator	
All patients	4549	100.0%	1844	100.0%
Total number of AE	716		281	
Patients with any AE	480	10.6%	197	10.7%
Patients with drug-related AE	182	4.0%	74	4.0%
Patients with serious AE	17	0.4%	4	0.2%
Patients with drug-related serious AE	1	<0.1%	0	0.0%
Patients with most frequent AE				
Headache	69	1.5%	22	1.2%
Nausea	56	1.2%	28	1.5%
Feeling hot	24	0.5%	8	0.4%
Dysgeusia	23	0.5%	7	0.4%

TABLE 3. Adverse Events by Dose of Gadobutrol

	Dose of Gadobutrol (mmol/kg Body Weight)*				
	≤0.09	>0.09–0.11	>0.11–0.21	>0.21–0.31	>0.31–0.51
No. patients	380 (100.0%)	2434 (100.0%)	679 (100.0%)	1009 (100.0%)	47 (100.0%)
Patients with any AE	46 (12.1%)	270 (11.1%)	78 (11.5%)	80 (7.9%)	6 (12.8%)
Patients with drug-related AE	17 (4.5%)	93 (3.8%)	27 (4.0%)	42 (4.2%)	3 (6.4%)
Total number of AE	72	414	111	111	8

*For the total of 4549 patients the dose distribution was 8.4% (≤0.09 mmol/kg body weight), 53.5% (>0.09–0.11 mmol/kg body weight), 14.9% (>0.11–0.21 mmol/kg body weight), 22.2% (>0.21–0.31 mmol/kg body weight), and 1.0% (>0.31–0.51 mmol/kg body weight).

with a range from 2 to 93 years. In the gadobutrol group, 58.5% of the patients were male. Most patients were white (64.8%), followed by Asian (27.3%). The demographic data of the gadobutrol group were similar to those of the comparator group (Table 1). Within the gadobutrol group, mean values of all demographic characteristics were similar over all dose groups (results not shown).

AEs Reported in the Clinical Trials

Of the 4549 patients who received gadobutrol, 480 (10.6%) patients reported 716 AEs independent of drug relationship. In the comparator group, with 197 (10.7%) of 1844 patients who reported 281 AEs, the incidence was similar. Most frequently reported AEs were headache, nausea, feeling hot, and dysgeusia (Table 2), regardless of the administered contrast agent. For the majority of the patients in the gadobutrol group (95.4%), their AEs were of mild intensity (for 350 of the 480 patients with AE, 72.9%) or moderate intensity (108/480, 22.5%); AEs of severe intensity were reported for 4.6% (21/480) of the patients; for one patient the severity assessment was not given.

Of the 4549 patients who received gadobutrol, 182 (4.0%) patients reported a total of 240 AEs assessed as drug-related. With 74 of 1844 patients (4.0%), the pattern and incidence of related AEs was the same in patients who received a comparator contrast agent (Table 2).

Increasing doses of gadobutrol did not lead to an increase in the AE incidence (Table 3). At any of the evaluated doses, the incidences of AEs and related AEs were similar. For the dose groups from ≤0.09 up to >0.21–0.31 mmol/kg body weight, incidence rates for related AEs were approximately 4.0%, with the lowest rate recorded for the largest group of patients who had received gadobutrol at the recommended standard dose of 0.1 mmol/kg body weight (3.8%). With 3 (6.4%) of 47 patients reporting related AEs in the small group of patients who had received higher than the approved dose of gadobutrol (>0.31–0.51 mmol/kg body weight), no safety concerns arose.

The most common adverse drug reactions (for definition see Materials and Methods section) for gadobutrol with incidence rates ≥0.5% were headache, nausea, injection site reactions of various kinds, dysgeusia, and feeling hot (Table 4). Adverse drug reactions were usually mild to moderate in severity and transient in nature.

A total of 21 patients reported SAEs (17 patients/0.4% in the gadobutrol group, 4 patients/0.2% in the comparator group). Only 1 of the SAEs of the 17 patients in the gadobutrol group was considered as possibly drug-related by the investigator (crystallized urine). This patient (9-year-old white female) was diagnosed with pneumonia on the day of the study MR imaging. The patient was hospitalized and treated with antibiotics (amoxicillin/clavulanate potassium [Augmentin, GSK, Brentford, London, United Kingdom]), and crystallized urine was diagnosed one day later. After treatment with Ringer solution (5%), the urinalysis performed 2 days later did not reveal any abnormal laboratory values. Crystalluria is given as an AE in the summary of product characteristics for amoxicillin/clavulanic acid. As the event could also

be related to the use of this concomitant medication, the sponsor assessed this AE as not related to gadobutrol. All other SAEs were not considered to be related to gadobutrol, including the death (dyspnea and pleural effusion) of one patient.

Slightly reduced drug-related AE incidences were observed for older patients: 1.9%, 2.9%, and 3.6% for patients aged ≥80 years, 65–79 years, and 45–64 years, respectively, compared with 5.8% for patients from the pediatric study aged 2 to 17 years and 6.1% for patients aged 18 to 44 years.

The majority of the patients (2292/4549, 50.4%) received gadobutrol for the indication CNS. For this indication an AE incidence of 13.0% was reported, which was well comparable to that observed in the comparator group (13.8%, result not shown). For the other adult patient groups, incidence rates in the gadobutrol group were 4.9% to 8.0%. Incidences for gadobutrol-related AEs in adults were in a range of 0.4% (myocardial perfusion) to 4.6% (CNS). This did not indicate any special safety risk depending on the given indication (Table 5).

Safety and Tolerability in Special Populations

Safety and Tolerability in Patients With Renal Impairment

The degree of renal impairment was classified based on eGFR values prior to contrast administration. The 366 patients with severe

TABLE 4. Adverse Drug Reactions Occurring in ≥0.1% of the Patients Following the Administration of Gadobutrol

Adverse Drug Reaction	Incidence (%) [*]
Headache	1.5
Nausea	1.2
Injection site reaction (various kinds) [†]	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)	0.2
Erythema	0.2
Dyspnea	0.2
Paresthesia	0.1

*Adverse reactions that occurred with a frequency of <0.1% include hypersensitivity/anaphylactoid reaction, loss of consciousness, convulsion, parosmia, tachycardia, palpitation, dry mouth, malaise, and feeling cold.

[†]Injection site reactions (various kinds) comprise the following terms: Injection site extravasation, injection site burning, injection site coldness, injection site warmth, injection site erythema or rash, injection site pain, injection site hematoma.

TABLE 5. Incidence of AEs With Gadobutrol by Indication

Indication	Patients (N)	All AE		Related AE	
		Patients With AE (N)	AE Incidence (%)	Patients With AE (N)	AE Incidence (%)
Central nervous system (CNS)	2292	297	13.0	106	4.6
Liver and kidney	1139	72	6.3	40	3.5
Contrast-enhanced magnetic resonance angiography (CE-MRA)	754	60	8.0	27	3.6
CNS, Body or CE-MRA in pediatric patients	138	40	29.0	8	5.8
Myocardial perfusion	226	11	4.9	1	0.4

(<30 mL/min) and moderate (30 mL/min to <60 mL/min) renal impairment presented with similar incidence rates of related AEs (7.9% and 1.8%, respectively) as those patients considered to have a mild impairment (60 mL/min to <90 mL), a normal renal function (≥ 90 mL), or those with missing serum creatinine values (3.9%, 6.3%, and 2.3%, respectively, Table 6). Neither in the gadobutrol group nor in the comparator group were consistent trends of an increase in the AE incidence rate with an increase of the severity of renal impairment detectable.

In the individual trial including patients with renal impairment or patients on dialysis, in 5 (15.6%) of the 32 patients 8 AEs were reported within 72 hours after the injection of the contrast agent. None of these AEs was assessed as drug-related. No differences in AE profile and AE frequency were observed between the 2 gadobutrol doses administered (ie, 0.1 and 0.3 mmol/kg body weight). No clinically significant changes or trends in vital signs were observed following the administration of gadobutrol. Any clinically relevant changes in creatinine clearance or in other laboratory parameters were assessed as not related to the administration of gadobutrol, but were caused by the underlying diseases. In patients on hemodialysis, gadobutrol was dialysable and could be cleared from the blood almost completely (98%) within 3 dialysis sessions.

Safety and Tolerability in Patients With Hepatic Impairment

Degree of liver impairment was assessed by the level of ALT and AST before the injection of the contrast agent. AE incidence rates were 2.3% (for patients in whom liver function parameters were not given), 4.1% and 4.3% (for the 2 groups of patients with impaired liver function), and 5.1% (for patients with a normal liver function, ie, maximum of ALT or AST values ≤ 1.8 upper limit of normal range; for details see Table 6). These incidence rates were not different from the incidence of AEs in the entire population (4.0%) and did not suggest any effect of liver impairment on the safety of gadobutrol. Also, for the comparator contrast agents no increase in the AE incidence with increasing liver impairment could be seen (Table 6).

Safety and Tolerability in Patients With Cardiovascular Disease

The subset of patients with cardiovascular disease did not have a higher risk of having an AE than those without cardiac problems, neither in the gadobutrol group nor in the comparator group (Table 6). Safe use in patients with cardiovascular disease was further confirmed on analysis of a subgroup of patients who had severe cardiovascular disorders. Of those, 53 of 735 patients (7.2%) presented with any AE. The incidence of related AEs (16/735, 2.2%) was lower than that in the total population (182/4549, 4.0%).

No significant effect of gadobutrol was detected in any of the ECG variables (heart rate, QRS, PQ, QT interval, and QTcF). For

TABLE 6. Incidence of AE with Gadobutrol and Comparator Contrast Agent in Special Populations

	Gadobutrol (N = 4549)		Comparator (N = 1844)	
Renal impairment by eGFR*				
<30 mL/min				
No. patients	38	100.0%	5	100.0%
Patients with related AE	3	7.9%	0	0.0%
30–<60 mL/min				
No. patients	328	100.0%	132	100.0%
Patients with related AE	6	1.8%	3	2.2%
60–<90 mL/min				
No. patients	846	100.0%	416	100.0%
Patients with related AE	33	3.9%	18	4.3%
≥90 mL/min				
No. patients	1610	100.0%	761	100.0%
Patients with related AE	101	6.3%	42	5.5%
Missing				
No. patients	1727	100.0%	530	100.0%
Patients with related AE	39	2.3%	11	2.1%
Liver function†				
3.0 ULN < max (ALT or AST)				
No. patients	73	100.0%	29	100.0%
Patients with related AE	3	4.1%	0	0.0%
1.8 ULN < max (ALT or AST) ≤3.0 ULN				
No. patients	141	100.0%	53	100.0%
Patients with related AE	6	4.3%	0	0.0%
Max (ALT or AST) ≤1.8 ULN				
No. patients	2606	100.0%	1227	100.0%
Patients with related AE	133	5.1%	61	5.0%
Missing				
No. patients	1729	100.0%	535	100.0%
Patients with related AE	40	2.3%	13	2.4%
Cardiovascular disorder				
Present				
No. patients	1506	100.0%	435	100.0%
Patients with related AE	42	2.8%	18	4.1%
Not present				
No. patients	3043	100.0%	1409	100.0%
Patients with related AE	140	4.6%	56	4.0%

*Estimated glomerular filtration rate (eGFR) level immediately prior to injection; patients with eGFR >60 mL/min were considered to have a normal renal function.

†Baseline maximum values of alanine aminotransferase (ALT) or aspartate aminotransferase (AST); patients whose liver enzymes were <1.8 upper limit of normal range (ULN) were considered to have a normal liver function.

QTcF, mean changes were in the range of -0.7 milliseconds (1 day post injection) to 3.4 milliseconds (0–15 minutes post injection).

To thoroughly investigate cardiovascular safety, in addition to the 34 clinical trials of the integrated analysis, a 5-period crossover trial was performed including subjects without clinically significant abnormalities in ECG (normal sinus rhythm; QTc <450 milliseconds), renal function, laboratory tests, or physical examination. For the primary end point based on the data of 54 subjects with all 5 periods, the treatment difference (gadobutrol minus placebo) for the mean change (15-minute average) from baseline in QTcF following administration of all gadobutrol doses (0.1, 0.3, and 0.5 mmol/kg bw) was less than 5 milliseconds (and the upper bound of the 2-sided 95% confidence interval excluded 10 milliseconds). Gadobutrol has no impact on cardiac repolarization, as only a mean change greater than 5 milliseconds and an upper bound of the confidence interval of ≥ 10 milliseconds would have been of safety and regulatory concern.²⁰ With regard to all other evaluated parameters, including AE evaluation, there were no significant changes. The number of patients reporting any AE was comparable for placebo treatment and moxifloxacin treatment. The number of patients reporting AE after gadobutrol administration increased with increasing doses, an effect which was only observed in this study. The most common drug-related AEs were dysgeusia, injection site coldness/warmth, and nausea. No patient experienced arrhythmias, palpitations, syncope, or seizures after gadobutrol injection. For laboratory parameters and vital signs, no consistent patterns among individual parameters over time and no evidence of a treatment effect relative to placebo were found.

Safety and Tolerability in Patients With a History of Allergies/Anaphylactoid Reaction

Of the 4549 patients who received gadobutrol, 462 patients (10.2%) presented with a history of allergies, 33 patients (0.7%) thereof with a history of allergies to contrast agents. Of the 462 patients with history of allergies (including allergies to contrast media), 81 patients (17.5%) developed AEs compared with 399 (9.8%) of the 4087 patients without allergies in their medical history. Of the 33 patients with a history of allergies to contrast media 7 (21.2%) had any AE compared with 473 (10.5%) of the 4516 without such a history. Comparable results were seen on analysis of the percentage of drug-related AEs. Such events occurred in 7.6% of the patients with a history of allergies compared with 3.6% in those patients without any allergies and in 6.1% of the patients with a history of allergies to contrast media compared with 4.0% of the other patients without such allergies.

Allergic reactions within 24 hours after injection of gadobutrol were recorded for 6 (0.1%) of the 4549 patients. Only one of these patients, who had developed rash and pruritus of mild intensity, had a previous history of allergies. None of the patients with an allergic reaction had a previous history of allergies to contrast media.

Safety and Tolerability in Children (2–17 Years)

The safety profile of gadobutrol in children was evaluated in a separate study individually designed to evaluate safety in pediatric patients aged 2 to 6 years (46 patients), aged 7 to 11 years (44 patients), and aged 12 to 17 years (48 patients). A total of 62 AEs were recorded for 40 (29.0%) of the 138 patients up to 72 hours after the injection. Drug-related AEs occurred in 8 (5.8%) patients and included (by preferred term) dysgeusia, feeling hot, crystallized urine, headache, nausea, rash, rash pruritic, and pruritus.

Laboratory parameters showed no trend toward a substantial change from baseline to follow-up in any of the parameters evaluated in any of the 3 age groups.

The mean values of all vital signs showed comparable values within each of the 3 pediatric age groups at the different time points of evaluation. There was no evidence of a noteworthy systematic change from immediately before injection to any time point after injection of gadobutrol.

Other Safety Results

Vital signs showed no relevant trends or changes over time after injection of gadobutrol or one of the comparator contrast agents. Transitions from baseline in physical examinations were reported in 42 (0.9%) of the 4549 patients of the gadobutrol group, but for none of them this was a clinically significant abnormal finding. The majority of transitions were observed one day after injection in the dose group of >0.11 to 0.21 mmol/kg body weight. Laboratory values, evaluated at baseline and at different time points up to 7 days post injection, did not show any signs of changes or tendencies attributable to gadobutrol.

Postmarketing Safety Surveillance

During the worldwide postmarketing use since approval in 1998 up to September 2010, with an estimated use of gadobutrol by more than 5.7 million patients, there was a total of 1175 suspected adverse drug reactions reports involving gadobutrol. Of those, 858 cases (819 medically confirmed, 39 medically not confirmed) were classified as nonserious and 317 cases (309 medically confirmed, 8 medically not confirmed) were classified as serious case reports. The most serious adverse reactions reported with gadobutrol were cardiac arrest, respiratory arrest, anaphylactoid shock, and 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 AEs have been received in connection with inadvertent double dosing.

Postmarketing Safety Data Regarding NSF-Like Symptoms

Of special interest, when assessing the safety of gadobutrol is the possibility of occurrence of NSF as there have been reports of NSF associated with the use of GBCAs, predominantly in patients with chronic severe renal impairment (GFR <30 mL/min/1.73 m²) or acute renal insufficiency. During the entire reporting period up to February 2011, Bayer Schering Pharma has received 10 reports suggesting the development of NSF after a reported administration of gadobutrol, including 3 already published reports^{21,22} (An update on NSF can be found on the following web link: http://www.diagnostic-imaging.bayerscheringpharma.de/scripts/pages/en/auth/healthcare_professionals_area/services/nsf_safety_update/index.php). Based on all available but incomplete data and using the criteria described earlier in the methods section, an association of NSF-like symptoms to the reported administration of gadobutrol cannot be excluded in 3 of the overall 10 cases; in the other 7 cases insufficient information is available to confirm or exclude such an association, eg, due to the confounding use of other contrast media. In no case was a definite causal role of gadobutrol determined.

Postmarketing Safety Data Concerning Renal Impairment

Another topic of interest for GBCAs is their potential renal toxicity. This is different from the NSF topic presented before. During postmarketing, 3 cases of renal failure and nephropathy were reported in patients with previous renal impairment and multiple comorbidities including cardiac disorders, hypertension and diabetes, and within an implausible time frame from gad-

obutrol administration, as well as more plausible alternative explanations. In one additional case, renal pain and creatinine increase were observed on the same day as gadobutrol was administered. Renal failure after the administration of contrast agents usually starts 2 or 3 days later, although the beginning on the same day is not absolutely excluded. The information of preexisting renal situation is unknown in this case.

In conclusion, Bayer Schering Pharma has received isolated reports of renal impairment in patients with preexisting renal impaired function. In one case, the renal status was not reported. In no case was gadobutrol determined as the causative agent, either because the temporal relationship was not compatible and/or more plausible alternative explanations existed. The cumulative postmarketing experience in patients with renal impairment supports the safe use of gadobutrol in this special population when following the appropriate precautions as described in the label.

Postmarketing Safety Data on Hepatic Impairment

There are no indications for a particular risk on the liver or on liver function arising from the diagnostic use of gadobutrol in human beings. Cumulative analysis of postmarketing reports supports the current knowledge about the safe use of gadobutrol in patients with hepatic impairment. Of particular note, no case of hepatorenal syndrome attributed to gadobutrol administration was received since its first approval 1998.

DISCUSSION

Gadobutrol has been available for clinical use since 1998. The favorable safety profile of gadobutrol after analysis of more than 4500 patients enrolled in clinical trials is confirmed by the results from an analysis of more than 14,000 patients included in observational trials. Forsting and Palkowitsch²³ reported adverse drug reactions in 0.55% of the subjects. The most common adverse drug reaction was nausea (0.25%), followed by vomiting (0.05%), urticaria (0.04%), feeling of warmth, tachycardia, and wheals (0.03% each). The general safety profile was found to correspond well to the data published for other extracellular GBCAs such as gadopentetate dimeglumine,¹ gadoversetamide,²⁴ gadodiamide,²⁵ or gadoteridol.²⁶

Since 2006, NSF, a rare but serious and potentially fatal condition of probably multifactorial cause, has been associated with the use of GBCAs in patients with severe renal impairment and acute renal failure. The highest number of reports of NSF are associated with the administration of the linear, nonionic chelate gadodiamide, which belongs to the group of chelates considered the most susceptible to Gd dissociation and/or to transmetallation.^{27–30} The differences in the complex stability of different GBCAs may have an impact on their potential to trigger NSF. Despite the fact that the assessment of postmarketing reports is often hampered by incomplete clinical and histologic information and confounding factors like use of multiple agents, the NSF reporting frequency has been used by regulators to classify GBCAs.^{31,32} On the basis of European Medicines Agency-Committee for Medicinal Products for Human Use (EMA-CHMP) assessment, marketed GBCAs are grouped into 3 different NSF risk categories depending on their potential to trigger NSF with macrocyclic Gadobutrol allocated to the low risk group.³¹ Similarly, the ACR included gadobutrol in the low risk class in their guideline.³² While acknowledging that there are reports of NSF^{21,22} that fulfilled the histopathologic and clinical criteria formulated by a panel that included S. Cowper in patients who appeared to have received Gadovist alone, also all but one of committee members voted that a contraindication of the product in patients with severe renal impairment is not required during a recently held FDA Advisory committee on gadobutrol (January 2011).³³ None of the patients from any clinical trial administered

gadobutrol, including 366 patients with impaired renal function, has been reported to have developed NSF. A limitation of the integrated analysis relates to the limited follow up of a maximum of 7 days as none of the studies was designed to study long-term effects. To assess the magnitude of a potential risk of gadobutrol for triggering the development of NSF currently the GRIP study (available at: <http://www.clinicaltrials.gov/ct2/show/NCT00828737>) is ongoing. In this prospectively planned study, the safety of gadobutrol will be evaluated in 1000 patients of the potential risk population of patients with moderate to severe renal impairment. The GRIP study is designed as a long-term follow-up over a period of 2 years, thus encompassing a period considerably longer than the usual onset of NSF of days to months after administration of a GBCA and also longer than the extended follow-up of 18 months currently used by Bayer when assessing potential NSF reports.

The main route of elimination of gadobutrol is by glomerular filtration, which means that in renally impaired patients the process of elimination is prolonged. To ensure the safe use of gadobutrol, particular attention was paid to the renal tolerance of gadobutrol. Of the 4549 patients, 38 patients were severely and another 328 patients were moderately impaired in their renal function (defined by eGFR <30 mL/min and 30 to <60 mL/min, respectively). The safety results neither indicated any increase in incidence of AEs, nor any unexpected AE profiles attributable to gadobutrol. This is in line with the results of one of the 34 studies included in this integrated analysis, which had been specifically designed to evaluate patients with chronic renal failure (n = 11 patients) or end-stage renal failure requiring hemodialysis (n = 11 patients) using gadobutrol at doses of 0.1 and 0.3 mmol/kg body weight, respectively. No drug-related AEs were reported and markers for glomerular filtration were found unaffected by the use of gadobutrol. A safe use of gadobutrol was shown in patients with impaired renal function³⁴ and in patients on dialysis, where gadobutrol is effectively removed by 3 hemodialysis sessions,³⁵ as well as in patients with known or suspected renal lesions when compared with gadopentetate dimeglumine.³⁶ In the entire subgroup of patients with impaired renal function (1212 patients with eGFR <90 mL/min), a total of 42 patients (3.5%) had drug-related AEs. None was indicative for NSF.

The degree of liver impairment was classified based on the ALT/AST levels prior to contrast administration. The comparison of AE incidence rates in the 3 subgroups suggests that gadobutrol may be safely used even in patients with severe hepatic impairment (defined as ALT/AST levels higher than 3 times the upper limit of the normal range). This may also be inferred from the results of 1 study of the pool of 34 studies, in which patients with known or suspected liver lesions had been enrolled, although the presence of a liver lesion does not directly relate to an impaired hepatic function. In this study, the safe use of gadobutrol was shown with AE incidence rates of 3.4% (10/292 patients) in the gadobutrol group and 5.0% (24/280 patients) in the gadopentetate dimeglumine group; in each group 7 related AEs were recorded.³⁷

We conclude cardiac safety of gadobutrol as patients with cardiac disorders, even those with severe deteriorations, were not affected by the administration of the contrast agent. Detailed analysis of ECG results, both in the integrated analysis and in a so-called “thorough” QT-study, showed that QTcF changes were around 5 milliseconds with an upper limit of the confidence interval below 10 milliseconds, thus being below the threshold of any safety and regulatory concern.²⁰ This was further evaluated by incorporating a correction for hysteresis. A potential influence of gadobutrol on cardiac repolarization was excluded by Malik et al.³⁸ Despite a substantial heart rate acceleration within the first minute after administration, the authors showed by accurate hysteresis correction

that gadobutrol in doses up to 0.5 mmol/kg body weight has no clinically relevant effect on cardiac repolarization.

The subset of patients with a history of allergies or those with a history of allergies to contrast media had a slightly higher risk of having an AE than those without an allergic history. Our results show an overall very low rate of allergic reactions (0.1%) among all patients who have received gadobutrol, which is in agreement with previous results showing that allergic-like reactions to intravenously administered GBCA are rare (0.07%).³⁹

Most patients enrolled in the 34 clinical studies were adults (≥ 18 years of age). One of the 34 studies was specifically designed to assess the pharmacokinetics and safety of gadobutrol in children. The pharmacokinetic results confirmed the assumption that Gd is renally excreted in the pediatric population as known for adult patients. No difference in the pharmacokinetics of gadobutrol in the evaluated age groups (2–6 years, 7–11 years, and 12–18 years) was evident.⁴⁰ The incidence of related AEs was similar in pediatric patients and the total population (5.8% vs. 4.0%). The safety profile in children from 2 to 17 years gave no indications for any differences compared with the safety profile known for adult patients which is underlined by the systemic exposure values (AUC) being similar in adults and pediatric patients.

CONCLUSIONS

In conclusion, gadobutrol provides an excellent safety profile. The number of adverse drug reactions is low, both on analysis of data from prospectively planned clinical trials (>4500 patients) and on comprehensive analysis of postmarketing data (>5.7 million subjects). Gadobutrol has been demonstrated as safe and well tolerated overall and in special populations such as children, patients with renal impairment, hepatic impairment, cardiac disease or history of allergies, showing a safety profile comparable to other contrast agents. The potential of gadobutrol to trigger development of NSF in patients with severely impaired renal function has been classified as low.

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REFERENCES

- Niendorf HP, Alhassan A, Balzer TH, et al. Safety and risk of gadolinium-DTPA: extended clinical experience after more than 20 million applications. In: Felix R, Hosten N, Hricak H, eds. *Magnevist Monograph*. 3rd revised ed. Oxford: Blackwell Science; 1998.
- Bellin MF. MR contrast agents, the old and the new. *Eur J Radiol*. 2006;60:314–323.
- Frenzel T, Lengsfeld P, Schirmer H, et al. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Invest Radiol*. 2008;43:817–828.
- Staks T, Schuhmann-Giampieri G, Frenzel T, et al. Pharmacokinetics, dose proportionality, and tolerability of gadobutrol after single intravenous injection in healthy volunteers. *Invest Radiol*. 1994;29:709–715.
- Goyen M, Lauenstein T, Herborn C, et al. 0.5M Gd chelate (Magnevist) versus 1.0M Gd chelate (Gadovist): dose-independent effect on image quality of pelvic three-dimensional MR-angiography. *J Magn Reson Imaging*. 2001;14:602–607.
- Tombach B, Benner T, Reimer P, et al. Do highly concentrated gadolinium chelates improve MR brain perfusion imaging? Intraindividually controlled randomized crossover concentration comparison study of 0.5 versus 1.0 mol/L gadobutrol. *Radiology*. 2003;226:880–888.
- Thilmann O, Larsson EM, Björkman-Burtscher IM, et al. Comparison of contrast agents with high molarity and with weak protein binding in cerebral perfusion imaging at 3T. *J Magn Reson Imaging*. 2005;22:597–604.
- Schaefer FK, Schaefer PJ, Altjohann C, et al. A multicenter, site-independent, blinded study to compare the diagnostic accuracy of contrast-enhanced magnetic resonance angiography using 1.0M gadobutrol (Gadovist) to intraarterial digital subtraction angiography in body arteries. *Eur J Radiol*. 2007;61:315–323.
- Anzalone N, Gerevini S, Scotti R, et al. Detection of cerebral metastases on magnetic resonance imaging: intraindividual comparison of gadobutrol with gadopentetate dimeglumine. *Acta Radiol*. 2009;50:933–940.
- Hadizadeh D, von Falkenhausen M, Kukuk GM, et al. Contrast material for abdominal dynamic contrast-enhanced 3D MR angiography with parallel imaging: intraindividual equimolar comparison of a macrocyclic 1.0 M gadolinium chelate and a linear ionic 0.5 M gadolinium chelate. *Am J Roentgenol*. 2010;194:821–829.
- Voth M, Michaely HJ, Schwenke C, et al. Contrast-enhanced magnetic resonance angiography (MRA): evaluation of three different contrast agents at two different doses (0.05 and 0.1 mmol/kg) in pigs at 1.5 Tesla. *Eur Radiol*. 2011;21:337–334.
- Morelli JN, Runge VM, Vu L, et al. Evaluation of gadodiamide versus gadobutrol for contrast-enhanced MR imaging in a rat brain glioma model at 1.5 and 3 T. *Invest Radiol*. 2010;45:810–818.
- Balzer JO, Loewe C, Davis K. Safety of contrast-enhanced MR angiography employing gadobutrol 1.0 M as contrast material. *Eur Radiol*. 2003;13:2067–2074.
- Palkowitsch P, Voth M. Summary of the safety data for Gadobutrol and Gadofosveset. *Eur Radiol Suppl*. 2009;18(suppl 5):E47–E54.
- FDA US Food and Drug Administration. Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf. January 2006.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
- Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am*. 1987;34:571–590.
- Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006;21:1104–1108.
- Broome DR, Girgis MS, Baron PW, et al. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *Am J Roentgenol*. 2007;188:586–592.
- ICH E14. Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-arrhythmic drugs. *Guidance for Industry*. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002879.pdf. October 2005.
- Wollanka H, Weidenmaier W, Giersig C. NSF after Gadovist exposure: a case report and hypothesis of NSF development. *Nephrol Dial Transplant*. 2009;24:3882–3884.
- Elmholdt TR, Jorgensen B, Ramsing M, et al. Two cases of nephrogenic systemic fibrosis after exposure to the macrocyclic compound gadobutrol. NDT Plus Advance Access. Published online on March 19, 2010. Available at: <http://ndtplus.oxfordjournals.org/cgi/content/abstract/sfq028>. Accessed October 14, 2010.
- Forsting M, Palkowitsch P. Prevalence of acute adverse reactions to gadobutrol-A highly concentrated macrocyclic gadolinium chelate: review of 14,299 patients from observational trials. *Eur Radiol*. 2010;74:e186–e192.
- Brown JJ, Kristy RM, Stevens GR, et al. The Optimark clinical development program: summary of safety data. *J Magn Reson Imaging*. 2002;15:446–455.
- Aslanian V, Lemaigen H, Bunouf P, et al. Evaluation of the clinical safety of gadodiamide injection, a new nonionic MRI contrast medium for the central nervous system: a European perspective. *Neuroradiology*. 1996;38:537–541.
- Olukotun AY, Parker JR, Meeks MJ, et al. Safety of gadoteridol injection: US clinical trial experience. *J Magn Reson Imaging*. 1995;5:17–25.
- Marckmann P, Skov L, Dupont A, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol*. 2006;17:2359–2362.
- Thomsen HS. Nephrogenic systemic fibrosis: history and epidemiology. *Radiol Clin North Am*. 2009;47:827–831.
- Ledneva E, Karie S, Launay-Vacher V, et al. Renal safety of gadolinium-based contrast media in patients with chronic renal insufficiency. *Radiology*. 2009;250:618–628.
- Janus N, Launay-Vacher V, Karie S, et al. Prevalence of nephrogenic

- systemic fibrosis in renal insufficiency patients: results of the FINEST study. *Eur J Radiol.* 2010;73:357–359.
31. EMEA. Questions and answers on the review of gadolinium-containing contrast agents. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500015635.pdf. Accessed October 14, 2010.
 32. ACR Manual on Contrast Media. Version 7, 2010. Available at http://www.acr.org/secondarymainmenucategories/quality_safety/contrast_manual.aspx.
 33. Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting January 21, 2011. Available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM244442.pdf>.
 34. Tombach B, Bremer C, Reimer P, et al. Renal tolerance of a neutral gadolinium chelate (gadobutrol) in patients with chronic renal failure: results of a randomized study. *Radiology.* 2001;218:651–657.
 35. Tombach B, Bremer C, Reimer P, et al. Using highly concentrated gadobutrol as an MR contrast agent in patients also requiring hemodialysis: safety and dialysability. *Am J Roentgenol.* 2002;178:105–109.
 36. Tombach B, Bohndorf K, Brodtrager W, et al. Comparison of 1.0 M gadobutrol and 0.5 M gadopentate dimeglumine-enhanced MRI in 471 patients with known or suspected renal lesions: results of a multicenter, single-blind, interindividual, randomized clinical phase III trial. *Eur Radiol.* 2008;18:2610–2619.
 37. Hammerstingl R, Adam G, Ayuso JR, et al. Comparison of 1.0 M gadobutrol and 0.5 M gadopentetate dimeglumine-enhanced magnetic resonance imaging in five hundred seventy-two patients with known or suspected liver lesions: results of a multicenter, double-blind, interindividual, randomized clinical phase-III trial. *Invest Radiol.* 2009;44:168–176.
 38. Malik M, Hnatkova K, Schmidt A, et al. Correction for QT/RR hysteresis in the assessment of drug-induced QTc changes—cardiac safety of gadobutrol. *Ann Noninvasive Electrocardiol.* 2009;14:242–250.
 39. Dillmann JR, Ellis JH, Cohan RH, et al. Frequency and severity of acute allergic-like reactions to gadolinium-containing iv contrast media in children and adults. *Am J Roentgenol.* 2007;189:1533–1515.
 40. Hahn G, Sorge I, Gruhn B, et al. Pharmacokinetics and safety of gadobutrol-enhanced magnetic resonance imaging in pediatric patients. *Invest Radiol.* 2009;44:776–783.