CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201277Orig1s000

<u>OFFICE DIRECTOR MEMO</u>

MEMORANDUM DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/OND/ODE-IV

Date: 03/11/2011
From: Shaw T. Chen, M.D., Ph.D., Deputy Director, ODE-IV
To: File, NDA-201277
Subject: Approval of NDA 201277, Gadavist (gadobutrol injection), a contrast agent for magnetic resonance imaging of central nervous system

This is the ODE memo to concur with the approval of this NDA, as recommended by the Division of Medical Imaging Products. Gadavist[1] is a new gadolinium based contrast agent (GBCA), formulated as a 1.0 Molar solution of gadobutrol for injection, to be used in the magnetic resonance imaging (MRI) study of central nervous system (CNS).

Overall, the data submitted in this application support the approval of gadobutrol as a new GBCA of relatively lower risk for nephrogenic systemic fibrosis (NSF)[2]. It will carry the same GBCA class labeling and monitored by the spontaneous reporting system and other standard pharmacovigilance practices. The effectiveness of these regulatory controls and other professional education efforts is attested by the declining incidence of GBCA-related NSF since the implementation of such measures. Therefore, no further NSF-based post-marketing studies are required for this new GBCA.

As summarized in the Division Director's memo by Dr. Dwaine Rieves, reviews by relevant disciplines and facility/data inspections have all been completed. There are no outstanding issues identified in the reviews or inspection that may preclude the approvability of this application. Final approval of this NDA is pending further editing of labeling and agreement on the proposed deferral plan of pediatric studies.

Major regulatory and scientific issues of this NDA are summarized as follows.

Efficacy and Safety

The conclusion that gadobutrol is an effective contrast agent, as reached by the review team and the Division Director, is correct and concurred by the Advisory Committee (meeting of January 21, 2011). The advantage of adding gadobutrol over non-contrasted imaging is highly statistically significant ($p < 0.001$) for all 3 endpoints of image quality in both of the two trials. For the number of lesions detected, the studies were design to show non-inferiority of adding the new contrast agent, with contrasted imaging not worse by -0.35 for the difference. Such objective was fully met in one study (Study 124, 95% CI -0.07, +0.70), but not in the other (Study 123 95% CI -0.44, +0.78). Because the non-inferiority margin is arbitrary and the other 3 superiority endpoints in image quality are highly significant and consistent, this isolated borderline result in lesion counts does not affect the overall conclusion of the efficacy data.

Other than the risk of NSF (see below) and rare reports of anaphylaxis, there is no other serious safety issue. The safety profile of Gadavist is similar to that of other GBCAs.

[1] Gadavist is the final proprietary name approved by FDA. Gadovist, a trade name proposed earlier, may be used in other review documents.
[2] All GBCAs are classified as low or high risk for NSF in the class labeling change of 2010. See discussion below.

Relative Risk of Nephrogenic Systemic Fibrosis

As noted above, all GBCAs currently approved in the U.S. are divided into two subgroups in the class labeling changes of December, 2010. Members of the higher risk group are contraindicated for patients with renal impairment, and those of lower risk carry only a box warning for NSF. Determining the risk of NSF for gadobutrol relative to other GBCAs is the most important regulatory decision of this NDA. As delineated in the Medical Team Leader's review by Dr. Lucie Yang, there has been great effort to differentiate the GBCAs, in search of distinctive characteristics that can help predict the risk of NSF for specific GBCA. Many of the proposed mechanisms to account for the differential risks of NSF remain theoretical and have been subject to challenge because of the exceptions to the suggested rules[3]. However, as summarized in Table 1 and discussed below, while no single property can predict the NSF risk with complete confidence, several of them can be viewed collectively to arrive at a reasonable estimate.

Table 1*

GBCA	structure, charge	pK_{therm}	Stability pK_{cond}	Kinetic $t_{1/2}$ (hr)	Gd release %/day	animal model** nm /g	case^	dose million	rate^^
Omniscan+	chain, non-ionic	16.9	14.9	0.01	0.16	132	505	49	10.31
Optimark+	chain, non-ionic	16.6	15.0		0.44	47	35	3.5	10.00
Magnevist+	chain, ionic	22.1	18.0	0.16	0.16	36	179	105	1.70
Multihance	chain, ionic	22.6	18.4		0.18	7	2	7.5	0.27
Eovist	chain, ionic	23.5	18.7		0.07	--	0	0.4	< 0.8
Ablavar	chain, ionic	22.1	18.9		0.12	--	0	0.1	< 3.3
Prohance	macrocyclic, non-ionic	23.8	17.0	1.6	<0.007	1	2	15	0.13
Dotarem	macrocyclic, ionic	25.6	19.0	7.0	<0.007	2	1	22.4	0.04
Gadavist	macrocyclic, non-ionic	21.8	15.0	23.0	<0.007	2	2	6	0.33

* Compiled from FDA Medical Team Leader's Review, FDA Pharmacology/Toxicology Review, and a publication by Idee JM et al, Toxicology, 2008; 248:77-88
** Deposit of Gd, nmol per gram of rat skin, Day 35
^ unconfounded or single agent case, world-wide reports and distribution. For Gadavist, 2 cases identified by the sponsor and primary medical reviewer, and 3 by Dr. Yang (see also below).
^^ for 0 case reported, the estimate is < 1/ (3 x number of dose), see also discussion below
+ contraindicated for patients with renal impairment.

The current prevailing concept suggests that NSF is caused by the free gadolinium released from GBCAs. The stability of the chelation between the gadolinium ion and the ligands is thus critical for predicting the risk. The GBCA with the linear or chain ligands, especially the non-ionic, are considered most unstable, and with the highest risk of releasing free Gd and causing NSF. This stability is measured as dissociation constants, including thermodynamic K_{therm} and conditional[4] K_{cond}, and rates/extent of dissociation (kinetic stability in half life and percentage of free Gd released). The differences in stability appear to correlate with the amount

[3] In addition to those listed in Table 1, other properties of GBCA have been proposed, but not proven yet, to account for the difference in NSF risk, which include selective stability (competitive binding relative to other ions) and relaxivity (lower dose can be used for GBCA of higher relaxivity). As noted in Dr. Yang's review, an alternative hypothesis emphasizing stimulation of fibrotic process by the chelated Gd (not free Gd) has been proposed. She also cited a report showing that macrocyclic GBCAs are not necessarily more stable than the ones with linear ligands. And in addition, not all linear ionic GBCAs have the same NSF risk (e.g., Magnevist vs Multihance).
[4] Conditional stability is measure at physiologic condition. See below for further discussion on stability of Gadavist.

of gadolinium deposit in rat skin. Based on these characteristics, the Division has proposed that Gadavist belong to the lower risk group, a position concurred by the Advisory Committee.

For all hypotheses, the ultimate confirmation is the numbers of clinical reports of NSF. The identification of first 3 high risk GBCAs (Omniscan, Optimark and Magnevist) is likely due to the relatively high number of reported NSF cases. In contrast, the rates of NSF reports were mostly lower than 1 per million for the safer GBCAs[5]. However, the relative rates of case reports should be viewed with caution. Besides the inherent limitation of such calculation, the overall incidence of NSF has been declining over the years (older agents had more cases) and the newer agents are used less frequently in the renally impaired (not the same base for comparison) because of the new warning in the labeling (see Dr. Yang's review). Thus, the correlation between the available rates of NSF reports and risk of individual GBCA remains tenuous, and the physicochemical properties and testing in animal model are still the practical criteria to differentiate the risk of NSF.

In her review, Dr. Yang raised a concern about the true relative risk of Gadavist (Sections 3.2.2.2-3.2.2.3). She argued that the number of NSF cases reported for Gadavist is higher than other macrocyclic GBCAs (2 in 6 million vs 1 in (b) (4) for Dotarem)[6] , which may be due to its lower stabilities (see pK_{cond} in Table 1). The subtle differences in this parameter and also in pK_{therm} may suggest that for macrocyclic GBCAs, ionic is safer than non-ionic. For Gadavist, these stability constants are closer to that of the high risk group than other low risk GBCAs are.

The lower thermodynamic and kinetic stabilities are of concern, but the extreme low rate of release for Gd from Gadavist probably more than compensate for that disadvantage in the practical time scale (see Table 1), as shown by the long half life (23 hrs), percentage of Gd release per day (the accumulated release remains low after Day 15, <0.1%, Table 3 of Dr. Yang's review), and low deposit of Gd in rat skin after 35 days (which remains low after 1 year, at near the control level of 0.06 nmol/g, see FDA Pharmacology-Toxicology review). In terms of the rate of NSF reports, while it is nominally higher for Gadavist than Dotarem and maybe underestimated (as a newer agent, for reason noted above), the current number of reports for Gadavist is still within the range of other low risk GBCAs. It is thus concluded that, despite Dr. Yang's concern, Gadavist can be considered a lower risk GBCA. The number of new NSF cases should be monitored by the standard pharmacovigilance measures, and the labeling adjusted according to the new post-marketing finding.

Risk of Overdose

The sponsor has proposed to market Gadavist formulated at a concentration (1.0 M) double that of 5 other GBCA with the same indication for CNS imaging (0.5 M), with the same recommended adult dose of 0.1 mmol/kg. Prescribing physicians and pharmacy staff may thus administer twice the recommended dose if they assume by mistake that Gadavist has the same concentration and is to be given at the same volume as other GBCAs. Since the risk of NSF increases with the dose administered, the consequence of potential medication error is more worrisome than in other setting. Of 716 subjects enrolled in phase 3 trials, there are 7 cases of "mis-administration" with double dose of Gadavist. While it is comforting that none of these

[5] The rates were calculated as there is no other measure for comparison; it is not intended to be a rigorous mathematical exercise. The estimated rates should be compared in the order of magnitude, not numerically.
[6] See Dr. Yang's review. As some case descriptions are not clear, the reviewers have identified different number of NSF cases. Dr. Yang has determined that there are 3 cases of NSF for Gadavist.

cases resulted in NSF, 1% incidence of dosing error in clinical trials suggests that it will likely occur in the practical setting. Appropriate measures to minimize this risk have been developed in the labeling.

The sponsor claimed that using a formulation at higher concentration will enable a more rapid infusion to facilitate faster scan for dynamic imaging study. It resulted in more T_1 shortening and better image quality without sacrificing the safety. More concentrated formulation has been a goal in development of all GBCA and only possible now with Gadavist. Overall, the benefit of using more concentrated formulation outweighs the manageable risk of overdose.

Dose Reduction for the Renally Impaired

The FDA reviewer on clinical pharmacology has recommended that, based on the prediction from modeling, the dose of Gadavist be reduced from 0.1 mmol/kg to 0.03 mmol/kg for patients with severe renal failure (GFR < 30 ml/min) (see FDA Clinical Pharmacology Review). While this may reduce the risk of NSF, efficacy of this lower dose has not been studied in the specified patients group. Actually, there is evidence from a Phase 2 study (Study 308200, see NDA file, communication from Bayer, March 2, 2011) that in non-renal failure patients, a dose of 0.1 mmol/kg showed significant improvement in imaging quality over the 0.03 mmol/kg dose. There is thus a concern that in renal failure patients, dosing at 0.03 mmol/kg may not be adequate for diagnostic purpose and additional doses will be needed, results in higher exposure than a single dose of 0.1 mmol/kg. Similar observation on dose lower than 0.1 mmol/kg has been documented for another GBCA.

The Division review team has decided correctly not to reduce the dose for patients with severe renal impairment.

Conclusions

Gadavist is to be approved as a new GBCA for CNS MRI with relatively lower risk of NSF.

The labeling should carry a class box warning about NSF, but without contraindication for renally impaired patients. It is not necessary to reduce the recommended dose for patients with severe renal failure. Precaution for overdose by medication error should be emphasized and appropriate measures to minimize this risk should be included in the labeling.

cc:
ORIG: NDA- 201277
Director, ODE-IV
Director, DMIP
Deputy Director, DMIP
Deputy Director for Safety, DMIP

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/s/

SHAW T CHEN
03/11/2011

Summary Review for Regulatory Action

Date	February 27, 2011
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	201277
Applicant Name	Bayer HealthCare Pharmaceuticals, Inc.
Date of Submission	May 14, 2010
PDUFA Goal Date	March 14, 2011
Proprietary Name / Established (USAN) Name	Gadavist™ Gadobutrol Injection
Dosage Forms / Strength	Gadobutrol Injection is to be supplied in: -single use vials of 7.5 mL, 10 mL, 15 mL -prefilled syringes of 7.5 mL, 10 mL, 15 mL -a pharmacy bulk package of 30 mL, 65 mL Each mL of the solution contains 1.0 gadobutrol, (b) (4) calcium sodium butrol, (b) (4) trimetamol, (b) (4) HCL; all in WFI, no preservatives; vials and packages are available with and without RFID tags.
Proposed Indication(s)	Gadavist is a gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system
Action/Recommended Action:	Approval once labeling is finalized

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Barbara Stinson, DO & Lucie Yang, MD, PhD (Acting TL)
Statistical Review	Anthony Mucci, PhD (Acting TL)
Pharmacology Toxicology Review	Olayinka Dina, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	David Place, PhD & Eldon Leutzinger, PhD
Microbiology Review	Jessica Cole, PhD
Clinical Pharmacology Review	Christy John, PhD & Y. Moon Choi, PhD (TL)
DDMAC	Not consulted during this review cycle
DSI	Susan Thompson, MD
CDTL Review	Lucie Yang, MD, PhD
OSE/DMEPA	Cathy Miller, BSN & Zachary Oleszczuk, PharmD (TL)
OSE	Michael kieffer, PharmD & Peter Diak, MD (TL)
Pediatric and Maternal Health	Leyla Sahin & Karen Feibus, MD (TL)

Project Manager	Sharon Thomas, MS

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls

1. Introduction:

Bayer HealthCare submitted this New Drug Application to support the approval of gadobutrol injection, a product which has been marketed in Europe for approximately 10 years. Gadobutrol is a gadolinium-based contrast agent (GBCA) proposed for use as contrast enhancement in magnetic resonance imaging (MRI). To date, FDA has approved seven GBCAs for use in MRI. The proposed gadobutrol indication relates to the imaging of the central nervous system (CNS) and is worded in a manner consistent with that of the five approved GBCAs with the CNS indication:

"for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system."

Bayer HealthCare conducted two confirmatory phase 3 studies to support gadobutrol approval, each designed in a manner similar to those supporting the approval of other GBCAs. The study results demonstrated that gadobutrol enhanced MRI visualization of CNS lesions and anatomy. Safety findings were similar to those of other GBCAs and approval of gadobutrol was recommended by a January 21, 2011 meeting of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee. The predominant review observation was that gadobutrol is to be marketed as a 1.0 M solution, while most (but not all) other GBCAs are marketed as a 0.5 M solution. Labeling was developed to help minimize the potential for medication errors due to the difference in molarity between gadobutrol and most other GBCAs.

At the time of this review document's development, final labeling is pending as well as definitive deferral of the proposed pediatric study (0 to 2 age range) and the definitive acceptance of the proposed tradename, Gadavist. For these items, the preliminary review feedback is summarized below.

2. Background:

GBCAs are paramagnetic MRI contrast agents used to improve the visualization of body structures or vasculature. To date, FDA has approved seven GBCAs (five for a CNS indication, see Table 1). The agents contain gadolinium, a paramagnetic metal which must remain chelated within the agent to avoid toxic effects from the gadolinium.

Table 1. Gadobutrol and Currently Approved GBCAs

Trade name	Established name	Indication	Dose, adult mmol/kg	Molar	Chemical structure
Magnevist	gadopentetate dimeglumine	CNS, body	0.1	0.5	Linear, ionic
Prohance	gadoteridol	CNS	0.1	0.5	Macrocyclic
Omniscan	gadodiamide	CNS, body	0.1	0.5	Linear, non-ionic
Optimark	gadoversetamide	CNS, liver	0.1	0.5	Linear, non-ionic
Multihance	gadobenate dimeglumine	CNS	0.1	0.5	Linear, ionic
Eovist	gadoxetate	Liver	0.025	0.25	Linear, ionic
Ablavar	gadofosveset	Aorto-iliac vessels	0.03	0.25	Linear, ionic
Pending	gadobutrol	CNS	0.1	1.0	Macrocyclic

GBCAs are widely acknowledged as critical to optimal MRI visualization of many parts of the body and are regarded as particularly valuable for tumor detection/anatomical characterization. To date, the predominant safety concerns have related to hypersensitivity reactions (anaphylactoid reactions, some fatal) and an association with nephrogenic systemic fibrosis (NSF).

In 2006 NSF, a scleroderma-like disease was associated with the use of GBCAs among patients with severe renal insufficiency. NSF produces characteristic skin lesions and a fibrotic process within multiple body organs which may result in death. There is no generally accepted treatment or cure. FDA and drug manufacturers have extensively modified labeling over the past four years in order to help minimize the NSF risk. These actions, as discussed at a December 2009 FDA advisory committee, have been credited with helping to reduce the occurrence of the condition since the initial reports surfaced in 2006/2007. In general, the reduction has been proposed to be related to enhanced screening for renal dysfunction and more judicious use of the agents.

In December, 2010, FDA approved revisions of GBCA labels to distinguish two major subsets of GBCAs: a group that is contraindicated for use among the highest risk patient population and a group that lacks this contraindication. The labeling change emphasized some magnitude of NSF risk for all the GBCAs in the vulnerable population (especially patients with severe, chronic kidney disease or acute kidney injury, the highest risk population). Consequently, all members of the GBCA class are anticipated to contain NSF risk information.

As shown in Table 1, gadobutrol has a “macrocyclic” structure which has been proposed to reduce the risk for liberation of gadolinium from the chelate and potentially lessen the risk for NSF, in comparison to other GBCAs. These concepts have not been verified and the relative importance of chemical structure in defining the NSF risk has not been established in comparison to other risk covariates (such as the extent of underlying kidney disease or agent dose).

Although the GBCA are viewed as a "class" based upon the same pharmacologic mechanism of action, the agents uniquely differ in multiple aspects (e.g., pharmacokinetics, pharmaco-dynamics, chemical structure, chelate-ion binding characteristics, etc). In this regard, FDA-approved labeling based upon a "GBCA class effect" did not mean that all GBCAs have identical risks and benefits nor did it mean that the magnitude of any individual risk (e.g., NSF) was the same for all members of the class. Instead, the NSF "class" risk indicated that the potential for the risk exists among all members of the drug class. Whether gadobutrol should carry a contraindication (for use among the most vulnerable patients with renal dysfunction) was a main topic at the January 21, 2011 advisory committee. The committee recommended that gadobutrol not carry this contraindication.

Overall, the supplied data support the approval of gadobutrol. The declining occurrence of NSF supports the effectiveness of GBCA class labeling as well as the impact of professional education by professional societies. Consequently, no NSF-based post-marketing studies are anticipated as requirements since the spontaneous reporting system and standard pharmacovigilance activities are assessed as reasonable to monitor for NSF occurrence.

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. David Place. The microbiology review was performed by Dr. Jessica Cole. The reviewers verified acceptable manufacturing procedures and recommended approval. No post-marketing studies were proposed. Dr. Place reports that all inspected facilities met expectations and the Office of Compliance regards all facilities as acceptable to support approval.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. Olayinka Dina, the pharmacology/toxicology reviewer who noted that there are no outstanding pharm/tox issues that preclude approval, beyond the development of acceptable labeling.

Gadobutrol was studied in standard rat and dog safety pharmacology studies as well as in modeling studies to estimate the risk for NSF. The drugs was found to be excreted unchanged (no metabolism) through the kidney. Toxicology findings were predominantly a dose-related, reversible vacuolation of the kidney proximal tubules. An NSF modeling study in rats showed gadobutrol did not produce lesions typical of NSF, unlike certain other GBCAs.

Gadobutrol was negative for mutagenesis in the ICH battery of required assays and carcinogenicity studies were not required. Reproductive toxicity studies were performed and the findings summarized in the proposed labeling.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval, although approval is contingent upon developing acceptable labeling pertaining to a possible reduction in gadobutrol dose among patients with severe kidney disease.

Gadobutrol has linear pharmacokinetics with increasing dose and is excreted unchanged by the kidney. The elimination half life is approximately two hours and blood protein binding is negligible. The company's study in pediatric patients (down to 2 years of age) supported the contention that dosing in pediatrics (over 2 years of age) is similar to that for adults.

A thorough QT electrocardiographic study was interpreted as reliable and did not demonstrate a signal for QT concerns.

6. Clinical Microbiology:

The microbiology reviewer recommended approval and I concur with her findings. No post-marketing studies were proposed.

7. Clinical/Statistical-Efficacy:

Dr. Barbara Stinson provided the main clinical review and Dr. Anthony Mucci provided the main statistical review. Dr. Lucie Yang provided a secondary clinical review. The reviewers noted that the main objectives of the two phase 3 clinical study were met. These studies were designed in a manner similar to that for other GBCAs in that the main outcomes were based upon comparisons of the visualization of anatomical structures. Specifically, patients who were undergoing MRI for suspected lesions were enrolled in the studies and underwent baseline, non-contrasted imaging followed by contrasted imaging. Paired (contrast plus non-contrast) images were compared to non-contrast images to assess the added value of the contrast. The studies used a central image interpretation process that was typical for contrast agent studies. Specifically:

The applicant conducted two phase 3 studies (Study 310123 and Study 310124). The review team generally refered to these studies as "Study 123" and "Study 124." The major design features were summarized within the study titles:

-Study 123: "A multicenter, randomized, double-blind, cross-over, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist) in patients referred to contrast-enhanced MRI of the central nervous system (CNS)". In this study, patients were to undergo an uncontrasted MRI followed by an MRI with gadobutrol and an MRI with Prohance (an approved GBCA) or vice versa; hence, this study enrolled only patients with glomerular filtration rates $\geq$ 60 mL/min/1.73m^2.

-Study 124: "A multicenter, open-label, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist) in patients referred for contrast-enhanced

MRI of the central nervous system (CNS)." In this study, patients underwent an uncontrasted MRI followed by an MRI with gadobutrol; patients were enrolled with glomerular filtration rates ≥ 30 mL/min/1.73m^2.

In both studies, three readers interpreted images at a centralized facility in a sequential, locked-read manner. The primary endpoints in each study involved comparisons of "paired uncontrasted + contrasted" images to uncontrasted images for four categories of anatomy visualization (number of lesions, contrast enhancement, border delineation and internal morphology). Superiority of the paired (uncontrasted + contrasted) images over uncontrasted images was required for success on three of the primary endpoint categories (enhancement, delineation, morphology) and noninferiority (paired versus uncontrasted) was required for the number of lesions comparison.

In Study 123, comparisons of gadobutrol to Prohance were secondary endpoints.

Study 123 enrolled 402 patients and included 336 subjects in the main efficacy analysis. Study 124 enrolled 343 patients and included 321 in the main efficacy analysis. The reasons for exclusion from the efficacy analyses were consistent with the prespecified criteria and typical for these types of studies.

In both studies, the anatomical visualization was scored on a scale (1 through 4) as shown below.

Table 2. Visualization Scores for Study 123 and 124

Score	**Efficacy Variables**		
	Contrast enhancement	Border delineation	Internal morphology
1	None	None	Poorly visible
2	Weak	Moderate	Moderately visible
3	Clear	Clear but incomplete	Sufficiently visible
4	Clear and bright	Clear and complete	Not applicable

The primary endpoint results (visualization scores/lesion number) are summarized below.

Table 3. Study 123 and 124 Primary Endpoint Results

Variable	Study 123			Study 124		
	C + U	U	Δ	C + U	U	Δ
Contrast enhancement	2.3	1.0	1.3	2.9	1.0	1.9
Border delineation	2.6	2.0	0.6	2.9	1.9	1.0
Internal morphology	2.6	2.0	0.6	2.4	1.6	0.8
Av number of lesions	8.3	8.1	0.2*	3.0	2.7	0.3

All visualization outcomes achieved statistical success (P < 0.001) except for average number of lesions in study 123 (*) where the confidence interval lower limit of – 0.44 did not meet the predefined margin of – 0.35. In Study 123, comparisons of gadovist and prohance visualization revealed similar outcomes for the two agents.

A supportive study examined pharmacokinetics in 138 pediatric patients older than 2 years of age. This study supported the ability to infer efficacy to the pediatric population older than 2 years.

8. Safety:

The most notable safety findings for gadobutrol were obtained from the post-marketing experience outside the US where both fatal anaphylaxis and NSF were uncommonly reported following exposure to approximately (b) (4) patients. Specifically, postmarketing reports included eight deaths attributed to anaphylaxis. NSF was reported among 10 patients following gadobutrol exposure. In eight of these reports, the patients had exposures to gadobutrol as well as at least one other GBCA. All 10 patients had renal dysfunction (five reported on hemodialysis).

Safety data were available from clinical trials (4549 subjects exposed to gadobutrol in phase 2 – 4 clinical trials, 333 subjects exposed in phase 1 studies). One subject in the phase 1 studies had an anaphylaxis reaction that consisted of cough, wheezing, desaturation and wheals that developed during administration of the drug. Medications (epinephrine, antihistamine) were administered and the symptoms resolved over the subsequent two hours. The clinical trial data showed that the most common adverse reactions were similar to those for other GBCAs and most common were headache (1.5%) and nausea (1.2%) among the patients within phase 2 – 4 trials.

9. Advisory Committee Meeting:

This application was presented to the Peripheral and Central Nervous System Advisory Committee on January 21, 2011. The committee voted (16 to 0) to recommend gadobutrol approval. With respect to the question as to whether or not labeling should include a contraindication for use of gadobutrol among patients at highest risk for NSF, the committee voted (15 to 1) to support no contraindication in the labeling.

10. Pediatrics:

Bayer HealthCare has requested a deferral of a pediatric study that they proposed to conduct in the population of patients less than 2 years of age. This proposal appears reasonable to the review team (because the drug is ready for approval in adults and conduct of the pediatric study will take some time/as well as refinement of the protocol). The pediatric review committee (PERC) is to provided definitive feedback in early March, 2011.

11. Other Relevant Regulatory Issues:

DSI inspection of the phase 3 clinical data detected no deficiencies that compromised the data integrity. Overall, the review team was consistent in its support for approval. No post-marketing commitments or post-marketing requirements are anticipated.

Other GBCAs approved over the last few years have included post-marketing requirements to perform studies that attempt to estimate the rate of NSF development among patients with renal dysfunction. These studies have proven particularly difficult to conduct because, according to the sponsors, the professional practice has changed such that fewer patients with important renal dysfunction undergo MRI with contrast (particularly since some agents are contraindicated in this population); hence, the available population for study has decreased since the original trial design development. Additionally, the power estimation for the original trial designs was based upon an estimated occurrence of 5% (as suggested in a study of gadodiamide); however, subsequent data has shown this estimate to be extraordinarily high and more recent rate estimates underscore the unfeasibility of sufficient patient recruitment. Accumulating data also support the contention that standard pharmacovigilance is sufficient for the estimation of NSF occurrence. Together, these observations support the acceptability of standard pharmacovigilance monitoring for NSF, including the plan for gadobutrol.

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/s/

RAFEL D RIEVES
02/27/2011