

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-090

MEDICAL REVIEW(S)

May 12, 2008

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Secondary Clinical Review

NDA	22-090
Established Name	Gadoxetate Disodium
Proposed Trade Name	Primovist Injection
Therapeutic Class	Diagnostic contrast agent for MRI
Applicant	Bayer Health Care Pharmaceuticals
Dosing Regimen	0.1 mL/kg intravenously as a bolus
Indication	Detection and characterization of focal liver lesions
Intended Population	Patients with known or suspected focal liver lesions
Reviewer Name	Louis Marzella M.D., Ph.D.

EXECUTIVE SUMMARY

Recommended regulatory action

The secondary reviewer agrees with the recommendation by Dr. Cynthia Welsh (primary clinical reviewer) that this NDA be approved.

Summary of efficacy and safety

Study protocols

The secondary reviewer agrees with Dr. Welsh that the four efficacy studies (protocol # 96129, 97160, 012387 and 014763) were adequately designed and controlled.

In all four studies, patients underwent non-contrast MRI followed by the administration of gadoxetate at a dose of 0.025 mmol/kg, with MRI performed immediately (the "dynamic" phase) and at 10 to 20 minutes (the "hepatocyte" phase). Patients also underwent computerized tomography with contrast examinations of the liver. To minimize bias, the principal efficacy outcome for each study was assessed by three independent radiologists blinded to clinical information. The radiologists viewed the MR images in a systematic, randomized, paired and unpaired fashion. An appropriate truth standard was used consisting of histology and intraoperative ultrasound for surgical patients and included various imaging modalities for patients for whom surgery or biopsy was not needed. Lesion tracking was used to verify correct lesion detection and the matching of MR imaging and truth standard was required.

The enrollment criteria of the efficacy studies provided for a study population that would reasonably permit extrapolation of study findings to the indicated population. The two detection studies shared an identical protocol and all patients had to undergo liver surgery; thus mostly patients with malignant focal liver lesions were enrolled. The two characterization studies also shared an identical protocol, however, a broader lesion type was represented. Patients had to have been scheduled for contrast biphasic (arterial and venous) spiral liver CT and have received an acceptable standard of reference (SOR) examination.

Studies 1 and 2 ("detection studies") assessed the sensitivity of pre-contrast MRI and gadoxetate-contrasted MRI for the detection of liver lesions, when each set of images was compared to the

reference. Studies 3 and 4 ("characterization" studies) assessed the correctness of liver lesion characterization by pre-contrast MRI and gadoxetate-contrasted MRI, when each set of images was compared to the reference. The PPS (per protocol set) included all patients who received the required dose of gadoxetate, who had no major deviations from the protocol, fulfilled the inclusion and exclusion criteria, completed the MRI procedure and had the Standard of Reference established.

A weakness of the design was that there was no prospective provision for assessment of specificity. Specificity of lesion detection was evaluated as a secondary analysis on liver segments. The total number of false positive lesions and the proportion of patients with at least one false positive lesion were also calculated. To assess sensitivity and specificity of characterization, the lesions were defined as dichotomous outcomes based on lesions type and were evaluated on a per lesion basis and on a liver segment level. Another limitation of the study design concerns the relatively short duration of safety follow up (approximately 24 hrs for the majority of study patients).

Efficacy findings

The secondary reviewer agrees with the conclusions by the primary clinical and statistical reviewers that the diagnostic effectiveness of gadoxetate has been demonstrated in this application.

The principal and various secondary efficacy outcomes were consistent in showing a diagnostic effect of gadoxetate within and across studies. The efficacy studies demonstrated that contrast Magnetic Resonance Imaging (MRI) using a single dose of gadoxetate (0.1 mL/kg intravenously as a bolus) improved the detection (studies 96129 and 97160) and characterization (studies 012387 and 014763) of liver lesions in patients with known or suspected focal liver lesions when compared with MRI without contrast.

No material study conduct issues were identified by the review of the data and by FDA inspection of selected clinical study sites. The diagnostic performance of non-contrast MR imaging was acceptable based on historical standards for MR and for CT imaging and allowed a valid assessment of gadoxetate efficacy. These secondary analyses were not intended to allow inferences to be made about the diagnostic performance of current MR vs. CT imaging

Safety findings

The secondary reviewer agrees with Dr. Welsh's assessment that gadoxetate has an acceptable safety profile.

Registration studies

A total of 1839 volunteers/patients was exposed to gadoxetate. Overall 28% of patients had cirrhosis and 8% had renal insufficiency. Approximately 2/3 of study patients had their final post-treatment physical examinations, laboratory testing and adverse event data collection at around 24 hrs. Approximately 1/3 had their last evaluation at around 72 hrs. These time intervals appear to be justified by the rapid clearance of the drug (approximately 90 min). Nevertheless the drug might induce reactions with delayed manifestations.

Of the 1755 patients, 181 (10%) experienced an adverse event. A total of 272 adverse events were reported and approximately 25% were judged to be moderate and 5% severe in intensity. Five of the severe AEs were also judged to be serious. Approximately one third of all AEs were judged by the investigators to be drug-related (attribution at least possibly related).

Six patients reported a total of ten serious AEs (SAE). None of the SAEs was attributed to the administration of gadoxetate by the clinical investigator. They occurred either as a complication of the underlying malignant disease (e.g. pulmonary embolism) or as complication of a previous

surgical intervention (e.g. peritonitis due to biliary leakage, hemothorax). Six patients died after the end of the study. Four of these patients died between 10 and 80 days after administration of gadoxetate. For two patients, no information about the time point of death is available. One patient suffered from recurrent pulmonary embolism. The first event was recorded as SAE. No causal relationship to the injection of the contrast medium was judged by the clinical investigators. All deaths were attributed to the underlying malignant disease processes in these patients. The most frequent AEs - independent of drug relationship - in the overall population of 1755 patients were: headache (1.1 %), nausea (1.1%), feeling hot (0.8%), back pain (0.6%) and dizziness (0.5 %).

ECG studies provided no indication of an effect of study drug administration on ventricular repolarization. No clinically important changes in mean or medium values for clinical chemistry, hematology and urinary parameters were observed. Individual changes of laboratory parameters in few patients occurred in liver enzymes, bilirubin, LDH and iron.

Postmarketing experience

A total of 12 adverse events were reported from marketing in Europe (approximately — patients exposed) and 6 adverse events were reported from a postmarketing observational study (N=471). Events included hypersensitivity reactions (urticaria, circulatory collapse, pruritus) tachycardia, dyspnea, agitation coronary syndrome, nausea, vomiting, confusion, dizziness. No cases of nephrogenic systemic fibrosis were identified.

Review procedure

The secondary reviewer read the FDA's primary clinical and statistical reviews, and evaluated the Sponsor's clinical study reports. The secondary reviewer also reviewed the package insert for gadoxetate.

Regulatory history

The following are the principal efficacy analyses requested by the agency.

- sensitivity and specificity analyses of the primary efficacy outcome
 - evidence that contrast did not worsen specificity of lesion detection would be necessary to support an improvement in the sensitivity of lesion detection
- comparison of non-contrast MRI images relative to paired non-contrast MRI and contrast MRI images
 - paired image presentation is consistent with clinical practice for MRI examinations and was recommended as the primary analysis
- assessment of adequacy of the performance of non-contrast MRI (e.g. by comparison to historical data)
 - expected diagnostic performance of gadoxetate comparator (non-contrast MRI) in patients with focal liver lesions was not pre-specified
- assessment of performance of contrast MRI by size of liver lesions and in comparison to spiral CT (the latter was required as entry criterion) to further define the diagnostic utility of gadoxetate

OVERVIEW OF FINDINGS BY VARIOUS DISCIPLINES

CMC and microbiology

No findings relevant to the clinical review were noted.

Toxicology

The principal finding of potential clinical importance was the prolongation of QT interval. The clinical data (including ECG tracings and adverse reaction data) showed no evidence that at clinically applicable doses gadoxetate increases the risk of cardiovascular adverse events.

Clinical Pharmacology

Pharmacodynamics

Gadoxetate disodium is a gadolinium-based MR-contrast agent. Its mode of action is a shortening the T1 relaxation time of hydrogen protons thus increasing the signal intensity in T1 weighted imaging sequences. A lipophilic moiety (EOB) allows the drug to enter the hepatocytes via membrane bound carriers. The drug is excreted into the bile by an organic anion transporter. Imaging is based on the increase in signal intensity in the dynamic phase (arterial, portal venous and equilibrium phase) followed by the parenchymal enhancement phase. Signal intensity reaches plateau after 20 min in the hepatocyte phase. The diagnostic outcomes were evaluated at this timepoint.

Pharmacokinetics

Renal and hepatic insufficiency

In end-stage renal failure (ESRF) the terminal half-life of gadoxetate was longer (20.4 h compared to < 3 h in all other groups studied) and the systemic exposure was higher (AUC was 5.6-fold higher). Moderate renal impairment and severe hepatic impairment had a modest effect on pharmacokinetic variables derived from the serum levels.

Compared to the control group, in moderate renal impairment (GFR, 30 – 50 mL/min) and severe hepatic impairment (Child-Pugh category C) the mean total clearance decreased by 28% and 33%, mean total AUC increased by 48% and 60%, respectively, and the terminal half-life increased slightly. Gadoxetate was found to be dialyzable. In a 3-hour dialysis session, which started 1 hour after the administration of the dose, about 30 % of the Gd-EOB-DTPA dose was removed by dialysis.

Drug interactions

Consistent with known mechanism of its hepatic disposition, only rifampicin, a known potent inhibitor of OATP significantly inhibited the hepatic enhancement at doses 3-5 times the recommended clinical dose of rifampicin indicating that liver uptake of Gd-EOB-DTPA in humans may be inhibited by coadministration of rifampicin.

Clinical and Statistical

Dose ranging studies

The dose of 100 $\mu\text{mol/kg}$ BW was too high since susceptibility effects led – after an initial signal increase - to a transient signal loss in healthy liver tissue. The doses up to 50 micromole/kg BW, however, showed a continuous increase of signal enhancement of the liver. Based on subjective image assessments including diagnostic confidence the dose of 25 micromole/kg BW was selected

Efficacy studies:

Objectives and design

The objective of the four efficacy studies was to determine if the MR examination with a single injection of gadoxetate improves detection (study 1 and 2) and classification (study 3 and 4) of focal

liver lesions. The studies were multicenter, multinational, open-label, intra-patient controlled comparisons of non-contrast MRI and contrast MRI images (using blinded reading) in patients scheduled for surgical resection of liver lesions.

Primary efficacy outcomes

The primary efficacy variable in the detection studies was sensitivity in liver lesion detection, defined as the relative frequency of matched lesions (i.e. correctly detected lesions verified by matching imaged lesions with the SOR) by patient. Hypothesis testing was based on the patients with any difference in sensitivity between combined pre- and post-contrast MRI and the pre-contrast MRI and was tested by the Wilcoxon signed rank test for each reader.

The primary efficacy variable in the characterization studies was the proportion of detected lesions with correct characterization (radiologic type). Hypothesis testing used a McNemar test with adjustment for clustering effect (multiple lesions in the same patient).

The primary analyses in all four studies were performed using the blinded reading, by comparing the sensitivity in lesion detection/proportion of correctly characterized lesions resulting from combined pre- and postcontrast MRI and pre-contrast MRI alone in the per-protocol population. The truth standard was histopathology for resected liver and ultrasound for the remainder of the liver or clinical follow-up (for non-surgical patients).

Secondary efficacy outcomes

Secondary variables for the lesion detection studies included the total number of false positive lesions as well as the proportion of patients with at least one false positive lesion (as measures of specificity). Because true negative lesions do not exist, a true negative segment was used as the unit for calculating specificity. Specificity was defined as the number of true negative segments divided by the number of true negative segments plus the number of false positive lesions.

Secondary variables for the lesion characterization studies included lesion classification (benign vs. malignant) and sensitivity/specificity of segment characterization by lesion type.

Patient disposition

The patient disposition across the two lesion detection and the two liver characterization studies was very similar (see table below). Patients were efficacy evaluable if they had SOR available and were excluded from the efficacy analysis for major protocol violations related to MRI image acquisition. The accounting of the excluded patients was complete and satisfactory.

Patient disposition in efficacy trials

Objective	Study number	Enrolled	Safety evaluable	Efficacy evaluable	Per protocol
Liver lesion detection	A00518	169	162	136	131
	A03779	172	169	138	131
Liver lesion characterization	A05742	235	231	202	182
	A01908	240	235	197	177

Lesion Detection Studies: No. 96129 and 97160

The secondary reviewer agrees with the clinical and statistical reviewer that the two studies support the diagnostic efficacy of gadoxetate. The designs of the two studies are identical and the results are found to be fully consistent across the two studies.

Primary efficacy variable

Study 96129. Of the 169 patients dosed, 131 had matched lesions verified by SOR. Of the 31 patients excluded from analysis 25 had missing/invalid SOR and 6 had major protocol deviations related mainly to MR image acquisition. Among the efficacy evaluable patients only 24 (as assessed by reader 1), 26 patients (reader 2) and 28 patients (reader 3) showed a difference in the number of matched lesions between combined pre- and post-contrast MRI and pre-contrast MRI. Out of these patients with a difference, 18 (75%), 19 (73%) and 19 (68%) patients had a higher number of matched lesions in combined pre- and post-contrast MRI. Only for one reader (#1) was this result statistically significant therefore, the study failed to meet its primary endpoint (see table below).

Study 97160. In the patients with any difference in sensitivity between the combined pre- and post-contrast and the pre-contrast MRI examinations (Reader 1: 31 patients, Reader 2: 29 patients and Reader 3: 41 patients) combined pre- and post-contrast MRI had a significantly higher number of matched lesions per patient in reader 1 and 3. The study therefore met its primary efficacy outcome.

Detection studies: Patients with any difference in sensitivity between combined pre- post- and pre-contrast MRI

Comparison	Study number	Reader 1	Reader 2	Reader 3
combined pre-and post-contrast MRI versus pre-contrast MRI	96129	18/24 patients (75%)	19/26 patients (73%)	19/28 patients (68%)
	97160	24/31 patients (77%)	21/29 patients (72%)	29/41 patients (71%)

Secondary analyses of the primary efficacy outcome on a per lesion basis showed increases in the total number of correctly detected liver lesions by 4 - 5% on average (with 95% CI excluding 0) in combined pre-and post-contrast MRI versus pre-contrast MRI. The difference in favor of pre and post was consistent across the readers in both studies for all three readers. Analyses by the FDA statistician showed that the improvement in lesion detection was primarily attributable to increase in lesion detection in patients with multiple lesions.

Principal secondary efficacy variable: Specificity

These analyses were performed to confirm that superiority in sensitivity was not accompanied by a deterioration in specificity.

False positive lesions by patient. The overall number of patients with at least one false positive lesion was numerically higher in post contrast MRI (33% and 31%) compared to precontrast MRI (30%, and 27%) in the two detection studies.

Specificity by liver segment

The assessment of liver segments (two lobes, or eight single liver segments or pooled segments) with at least one liver lesion was used to evaluate specificity. In the two detection studies the numerical increases in sensitivity were confirmed and were associated with no changes or small numerical decreases in specificity in the combined pre-and post-contrast / pre-contrast evaluation.

The table below shows the results of sensitivity analyses for study 96129 (similar results were found for study 97160). The proportion of by-patient false positive lesions and the sensitivity/specificity by liver segment are similar between pre-contrast and contrast images.

Assessment of specificity in lesion detection: study 96129

Examination	Reader 1	Reader 2	Reader 3
<u>pre-contrast MRI</u>			
Liver lobe: Sensitivity	86	88	82
Specificity	65	74	85
Patients with at least one false positive lesion	44	24	28
<u>combined pre-and post- contrast MRI</u>			
Liver lobe: Sensitivity	88	90	85
Specificity	73	74	71
Patients with at least one false positive lesion	39	28	35

Numbers are percentages

The secondary reviewer agrees with the primary reviewer that these analyses show no evidence of inflation of sensitivity (by “overcalling lesions”) and therefore strongly support the diagnostic efficacy of gadoxetate.

Other secondary analyses of clinical importance

Lesion classification and detection were examined to determine if the diagnostic performance for important lesions was adversely affected by gadoxetate. For lesion classification the blinded reader classified each lesion as either malignant, benign or non- not assessable. For lesion characterization the following were definition of focal liver lesions were used. Malignant: hepatocellular carcinoma, cholangiocarcinoma, metastasis, focal lymphoma. Benign: adenoma, focal nodular hyperplasia, hemangioma, abscess, focal liver fibrosis, regenerative nodule, focal fatty infiltration, focal sparing in fatty liver, hydatid cyst, liver cyst.

Of 302 SOR lesions, 172 (57%) were characterized as metastases, 41 (16%) as liver cysts, 31 (10%) as HCC, 18 (6%) as hemangioma and 8 (3%) as not assessable. The overall percentage of correctly characterized lesions was 51% for pre-contrast and 58% for pre- and post-contrast MRI. There was no evidence of inferior diagnostic performance by lesion type. The overall percentage of correctly classified lesions (benign or malignant) was 62% in pre-contrast MRI and 67% in pre- and post-contrast MRI.

Lesion characterization studies: No. 012387 and 014763

The secondary reviewer agrees with the clinical and statistical reviewer that the two studies support the diagnostic efficacy of gadoxetate.

The designs of the two studies are identical and the results are found to be fully consistent across the two studies. The proportion of detected and correctly characterized lesions was higher for combined pre and post-contrast imaging compared with pre-contrast.

Primary efficacy

Study 012387. Of 235 patients enrolled, 231 patients completed treatment with gadoxetate, 202 had a valid SOR, and 182 met prespecified protocol criteria. The proportion of correctly characterized proven lesions increased for all 3 readers with combined MRI and was significantly greater than with pre-contrast MRI alone for 2 of the 3 readers (see table below).

Study 014763. Of 240 patients enrolled, 235 patients completed treatment with gadoxetate, 197 had a valid SOR and 177 met prespecified protocol criteria. The proportion of correctly characterized proven lesions was significantly greater with combined MRI than with pre-contrast MRI alone for 2 of the 3 readers (see table below).

Proportion of Correctly Characterized Lesions

		Study 3 N=182	Study 4 N=177
Diagnostic Procedure	Reader	Proportion correct (%) **	Proportion correct (%) **
Pre-contrast MRI	Reader 1	51	60
	Reader 2	59	64
	Reader 3	53	48
Combined pre- and EOVIST-contrast MRI	Reader 1	67	61
	Reader 2	76	76
	Reader 3	58	67
Difference: Combined pre- and EOVIST-contrast MRI minus Pre-contrast MRI (95% confidence interval)	Reader 1	16 (7, 25)*	1 (-7, 10)
	Reader 2	17 (9, 25)*	11 (5, 18)*
	Reader 3	5 (-2, 12)	19 (11, 27)*

* = statistically significant improvement

** proportion of correctly characterized lesions with respect to the reference.

Secondary efficacy

Lesion classification

The number of correctly classified lesions was higher for combined pre- and post-contrast MRI than for precontrast MRI alone for 2 of the 3 readers. For specificity the values were similar with combined MRI versus pre-contrast MRI for 2 readers and numerically higher with combined MRI for the third reader.

The diagnostic performance across the lesion types seen most commonly (metastases, hemangioma, FNH and liver cyst) was examined and no evidence of interference by gadaxetate with diagnostic performance was found.

NDA 22-090 Gadoxetate disodium
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L Marzella

Recommended postmarketing actions

The Sponsor has agreed to conduct a registry study to further assess the risk of nephrogenic systemic fibrosis. The study protocol and performance timelines are acceptable.

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Liberio Marzella
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Rafel Rieves
5/19/2008 02:17:05 PM
MEDICAL OFFICER

CLINICAL REVIEW

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Established (USAN) Name Gadoxetate Disodium
(Proposed) Trade Name Gadoxetate Disodium Injection
Therapeutic Class MRI diagnostic contrast agent
Applicant Bayer Health Care Pharmaceuticals

Priority Designation S

Formulation 0.25 mmol/ml solution
Dosing Regimen single use, 0.025 mmol/kg IV
Indication Gadoxetate Disodium is a gadolinium based Contrast agent indicated for intravenous use in T1 weighted magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in adults with known or suspected focal liver disease.

Intended Population Adult patients with known or suspected focal liver disease

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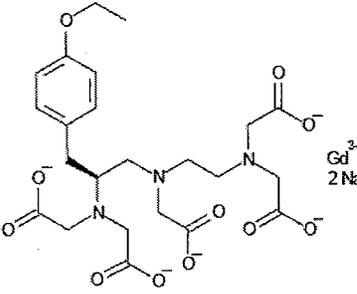
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2 Introduction and Regulatory Background

2.1 Product Information

- Gadoxetate Disodium is a liver specific, intracellular, intravenous diagnostic contrast agent for use in MRI that exhibits high relaxivity and provides contrast of the liver in the T1 imaging mode.
- The non-proprietary (USAN) name of the product is Gadoxetate Disodium.
- The proposed trade name is Gadoxetate Disodium Injection.
- Chemical class: This product is new molecular entity (NME). It is a derivative of Gd-DTPA in which a lipophilic moiety was added that results in weak protein binding and enables Gadoxetate Disodium to enter hepatocytes via membrane bound carriers (organic anion transporting polypeptides).

Structural formula	
Molecular formula	C ₂₉ H ₂₈ N ₃ O ₁₁ ·Gd·2Na
Relative molecular mass	725.72

- Pharmacological class: The product is a gadolinium-based T1 MR contrast agent that shortens the T1 relaxation time of hydrogen protons which causes an increase of signal intensity in T1 weighted imaging sequences. There are three phases of enhancement: arterial, followed by the portal venous phase, and finally, the parenchymal enhancement phase. It also visualizes the excretion into the biliary system with subsequent enhancement of the intra- and extra- hepatic biliary ducts.
- Proposed indication: For use in magnetic resonance imaging (MRI) of the liver in adult patients _____ the T1-weighted images _____ the detection, _____ and characterization of focal liver pathologies _____ in a pre-surgical evaluation.
- The proposed dose is 25 μmol/kg. The excretion route is 50% renal and 50% biliary.

- The proposed target population: Patients referred for MRI as part of the pre-surgical/pre-interventional assessment, in whom the lesion detection and the radiological characterization of the detected lesions is clinically relevant:
 - Patients with known primary cancer outside the liver and known or suspected metastatic spread into the liver for determination of surgical strategy or planning for neoadjuvant chemotherapy or palliative interventional strategies
 - Patients with suspected or known primary liver cancer for detection and definition of extent of disease in the liver
 - Patients with newly detected lesions and the necessity to get information about the classification and exact lesion type for therapy planning.

2.2 Tables of Currently Available Treatments for Proposed Indications

1. There is only one liver specific, intracellular MRI contrast agent approved and marketed in the U.S. (from the label):

Feridex (ferumoxide injectable solution – note: this is not a gadolinium containing agent) is a superparamagnetic iron oxide associated with dextran that is indicated for IV administration as an adjunct to MRI (in adult patients) to enhance the T2 weighted images (as opposed to T1 weighted images for Gadoxetate Disodium) used in the detection and evaluation of lesions of the liver that are associated with an alteration in the reticuloendothelial system (RES). It is taken up by cells of the RES rather than by hepatocytes as is the case with Gadoxetate Disodium. Feridex I.V. shortens the relaxation times for nearby hydrogen atoms and reduces signal intensity in normal tissues. This results in signal loss on mid T1/T2 or strongly T2-weighted images. Tissues with decreased RES function (e.g., metastases, primary liver cancer, cysts and various benign tumors, adenomas, and hyperplasia) retain their native signal intensity, so the contrast between normal and abnormal tissue is increased.

The recommended dosage of Feridex I.V. is 0.56 milligrams of iron (0.05 mL Feridex I.V.) per kilogram of body weight that is diluted in 100 mL of 5% dextrose solution and given over 30 minutes. Post-contrast imaging may begin immediately after the dose is infused and may be performed up to 3.5 hours after the end of the infusion. T2-weighted pulse sequences provide the maximum contrast effect.

2. There are five extracellular, non-liver specific (save Optimark), MRI contrast agents available in the U.S. They have the following indications (from their respective labels):

a. **Magnevist** is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the brain, spine and associated tissues as well as visualization of lesions with abnormal vascularity of the head and neck and the body (excluding the heart).

b. **Multihance** is indicated for IV use in MRI of the CNS in adults to visualize lesions with abnormal blood-brain barrier or abnormal vascularity in the brain, spine and associated tissues.

c. **Omniscan** is indicated for IV use in MRI to visualize lesions with abnormal vascularity in the brain, spine and associated tissues. It is also indicated for IV administration to facilitate the visualization of lesions with abnormal vascularity within the thoracic (non-cardiac), abdominal, pelvic cavities, and the retroperitoneal space.

d. **Optimark** is indicated for use in MRI in patients with abnormal blood-brain barrier or abnormal vascularity in the brain, spine and associated tissues. It is also indicated for use with MRI to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography (CT).

e. **Prohance** is indicated for use in MRI in adults and children over 2 years of age to visualize lesions with abnormal vascularity in the brain, spine and associated tissues as well as for use in adults to visualize lesions of the head and neck.

Note the following:

- a. That only Magnevist and Prohance are approved for specific pediatric cases (ages >2).
- b. Optimark is approved for liver imaging of patients with abnormalities seen on CT.

3. Other imaging modalities:

a. **Ultrasound**: The first diagnostic test utilized is usually ultrasound. This test is operator dependent and used to make a final diagnosis in limited situations.

b. **Contrast enhanced computed tomography**: The enhancement of the parenchyma assists in the detection of liver lesions while the capability to capture each phase of the perfusion of liver lesions (arterial phase, portal venous phase) is used to classify and characterize liver lesions.

c. **MRI**: for liver lesions may be performed with and without contrast enhancement using extra-cellular contrast agents (Optimark - known to help in the detection mainly of hypervascular liver lesions) for lesion visualization and characterization and by liver specific MR contrast agent (Feridex).

2.3 Availability of Proposed Active Ingredient in the United States

This drug product is a new molecular entity and is not currently marketed in this country.

2.4 Important Safety Issues With Consideration to Related Drugs

In 2006, the Agency issued a Public Health Advisory notice and recommended that the manufacturers of gadolinium containing products send a Dear Healthcare Provider letter regarding the potential development of Nephrogenic Systemic Fibrosis (NSF) that has been associated with gadolinium containing MRI contrast agents when used in patients with severely impaired renal function ($GFR < 30 \text{ mL/min/1.73 m}^2$). Additionally, class labeling changes for these products included the addition of a black box warning and changes to the Warnings section of the label.

There have been no reported cases of NSF associated with Gadoxetate Disodium either in the countries where the product is approved and marketed or from the clinical trials conducted in the U.S. However, it is not clear how many, if any, patients with severe renal impairment were included in the studies for approval abroad or exposed in the global market. This reviewer recommends that the manufacturers of Gadoxetate Disodium should include the 'Changes Being Effected' class labeling changes as recommended by the Agency for the other gadolinium containing products as well as participate in ~~_____~~ post-marketing risk management/registry study ~~_____~~ even though a) no cases of NSF have been reported with use of Gadoxetate Disodium and b) Gadoxetate Disodium has both renal and hepatic pathways for elimination of the drug. The manufacturer is aware of these post-marketing requirements ~~_____~~

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The pivotal phase 3 studies issues regarding primary efficacy variable (sensitivity and specificity), statistical evaluation of the primary efficacy variable, and patient population have been discussed with the sponsor via meetings, teleconferences and written communication.

The original IND was submitted December 19, 1997. Meetings were held March 26, 1998 to discuss the proposed clinical development plan; and November 16, 2000 to discuss revised indication for Gadoxetate Disodium and to seek confirmation from the Agency that the sponsor's phase 3 clinical development plan could support the revised indication. No further meetings were held until a teleconference was held January 19, 2006 when the Agency commented on weaknesses in their completed phase 3 studies and proposed suggestions for post-hoc analyses that could be performed and submitted to the Agency to strengthen their application. A Type C meeting was held April 20, 2006 at which time the Agency reiterated the phase 3 study weaknesses and proposed suggestions. The sponsor subsequently submitted a NDA that did include post-hoc analyses as suggested by the Agency.

From the beginning of the development of the clinical program, the division has made comments regarding the primary efficacy endpoint (sensitivity and specificity as opposed to accuracy), various image presentations including pre MRI vs. post MRI vs. combined pre and post MRI in

paired and unpaired reading format – *Note that the division initially recommended the PEE be unpaired pre compared to unpaired post. The current divisional thinking is that the PEE should be (both paired and unpaired) pre vs. combined to reflect actual clinical use*, study design (lack of prospective imaging criteria for lesion characterization and classification).

2006 April 20 Type C meeting – discussion of clinical development and CMC issues.

The Division reviewed the meeting package and had the following clinical recommendations for the studies for liver lesion detection and characterization. See CMC review for details of CMC issues.

- a. Assess the contribution of the test agent to standard diagnostics for liver lesions. A comparison of contrast MRI to the other diagnostic modality (e.g. spiral enhanced CT), and to the truth standard, histopathology, and final clinical diagnosis (for lesions that do not require biopsy) might provide a more convincing demonstration of clinical utility.
- b. An efficacy endpoint consisting of lesion detection alone in a patient population with known or suspected liver lesion does not provide a sufficient assessment of the utility of the test diagnostic. Detection and characterization of the lesions would provide a more meaningful assessment of diagnostic performance in this setting.
- c. An assessment of sensitivity in detection and diagnosis is an incomplete measure of clinical utility. We recommend that the data be analyzed for the sensitivity and specificity of MRI compared to the standard diagnostic and to the truth standard for lesion detection and characterization in various liver segments.

This information was also reiterated to the sponsor in September 2006 via fax and again in the 74 day letter in September 2007.

The sponsor has attempted to address our comments by performing post hoc analyses, incorporating specificity, lesion size, and comparison to contrast enhanced CT.

2.6 Other Relevant Background Information

Gadoxetate Disodium was first approved in Sweden in March 2004; with subsequent approval via Mutual Recognition Procedure in 25 EU countries for the indication “*Gadoxetate Disodium is indicated for the detection of focal liver lesions and provides information on the character of lesions in T1-weighted magnetic resonance imaging (MRI). This medicinal product is for diagnostic use by intravenous administration only*”. As of the submission date of this application, Gadoxetate Disodium is approved in 34 countries, including the extended EU, Switzerland, Australia, South Africa and several Asian countries. Gadoxetate Disodium was submitted in Japan in July 2004. Approval is pending at the time of this review.

2.7 Pediatric Waiver

The applicant has requested a pediatric waiver for ages 0 to 17 years based upon the following reasons:

- Gadoxetate Disodium Injection is unlikely to be used in a substantial number of pediatric patients due to the low incidence of focal liver lesions;
- Necessary studies are impossible or highly impractical because the number of such patients is so small or geographically dispersed.

Discussion:

- The indication for Primovist, as submitted in the application, is for _____ with liver masses and was therefore not studied in the pediatric population.
- Malignant liver tumors are rare in the U.S. pediatric population. Primary hepatic malignancies in children are most commonly either hepatoblastoma (typically <5 years of age) or hepatocellular carcinoma (typically 15-19 years of age). Benign liver tumors (hemangiomas and hamartomas) are also rare in the pediatric population.
- The SEER 2000-2003 data is ~2/million for liver malignancies and ~2/million for benign liver masses.
- Estimated number of pediatric (age < 18 years) contrast enhanced imaging studies (MRI and CT) of the liver performed in the U.S. according to market research supplied by _____ to the applicant:

	2004	2005	Until June 2006
MRI			
Total number of procedures			
Age < 18 years	/	/	/
CT			
Total number of procedures			
Age < 18 years			

Due to the rarity of liver tumors in the pediatric population in the U.S. and the small number of contrast enhanced MRI scans performed, it would be very difficult to perform efficacy studies in the pediatric population.

However — contrast enhanced liver studies were performed in 2005. It would therefore be feasible over a number of years for the applicant to perform studies to evaluate pharmacodynamic/pharmacokinetic endpoints and initial safety studies. Therefore, this reviewer recommends a deferral for these endpoints.

The waiver request was evaluated by the Pediatric Review Committee (PeRC). The committee denied the sponsor's request for a pediatric waiver and recommended that the reviewing division seek a consult from Division of Drug Oncology (DDOP) regarding the necessity for PD/PK studies for this product. The committee's opinion was that while it is true that HCC are rare in the pediatric population, liver abnormalities that might need to be evaluated (e.g., benign masses, hepatoblastoma) exist.

Consultation was sought from DDOP who recommended:
 Based on these considerations and the purported effect of this contrast agent in optimizing MRI imaging of the liver, the reviewing division is encouraged to grant a deferral as opposed to a waiver of pediatric studies. The possibility of conducting one or more studies to explore relationships between dose, PK, and MRI imaging characteristics in children with hepatoblastoma and hepatocellular carcinoma should be discussed with the NDA applicant.

Recommendation:
 The DDOP recommendation was forwarded to the PeRC for review. The results of the review are pending at the time of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted regarding site visits for this NDA. The pivotal studies utilized multiple study centers that enrolled 30 patients or less. The following sites were suggested for inspection to DSI based upon protocol violations and adverse events as reported by the applicant in the study reports:

Site # (Name and Address)	Report #/ Protocol #	Number of Subjects	Indication
Universitätsklinikum Großhadern München Marchioninstr: 15, 81366 München, FRG	A00518 96129/98148	23	Protocol deviations and adverse events
University of Michigan Hospitals 1500 East Medical Center Drive Ann Arbor, MI 48109-0030, USA	A03779 97160/98146	20	Protocol deviations and adverse events
Universita La Sapienza Viale Regina Elena 324, 00161 Rome, Italy	A05742 12387/303222	15	Protocol deviations and adverse events
Thomas Jefferson University Hospital 132 South 10 th Street Philadelphia, PA 19107, USA	A01908 14763/303308	14	Protocol deviations and adverse events

Site # (Name and Address)	Report #/ Protocol #	Number of Subjects	Indication
UCLA Department of Radiological Sciences 10833 Le Conte Avenue Los Angeles, CA 90095-1721, USA	A01908 014763	25	Protocol deviations and adverse events

The DSI report revealed no major deficiencies that could compromise the integrity of the data.

3.2 Compliance with Good Clinical Practices

These pivotal studies were performed in accordance with acceptable clinical standards (e.g. standard of reference was patient specific as determined by the nature of their lesion). The protocol violations in these studies mainly centered around incomplete follow up, missing imaging sequences that excluded the data from the primary efficacy analysis, and incorrect study drug administration (e.g. +/- 10% of prespecified dosage). The sites with the greatest number of major protocol violations were placed on the inspection site list. The protocols contained a statement that informed consent would be required and obtained by the study investigators and subsequently kept on file. As reported by the Special Government Employee who reviewed the efficacy data, the imaging procedures and the image acquisition protocols were standard and the blinded reading of the images was well controlled.

3.3 Financial Disclosures

Bayer HealthCare Pharmaceuticals Inc. submitted a list of all clinical investigators who participated in the clinical studies. The applicant certified that no financial arrangements with any of the listed investigators had been made where the study outcome could affect compensation. The compensation paid to any of the investigators for their conduct of the covered studies was independent of the results of the study.

Please note that the final rule requiring of the financial disclosure by clinical investigators was published on February 2, 1998. The detection studies, study 96129 and study 97160, started in September 1998. The sponsor made an effort to request financial information covering the whole study period from the investigators at the end of the study. Reminder letters from the sponsor to the investigator are kept on file. They found that there were 58 investigators out of ~280 investigators (47 of the investigators are from the detection studies and 11 are from the characterization studies) for whom Bayer HealthCare Pharmaceuticals cannot certify their personal and disclosable financial interest in the Sponsor. The total number of patients enrolled in three of the centers was small (8 patients enrolled by 18 investigators).

Given the overall small number of investigators (58 out of 280) for which no personal and disclosable financial interest in the Sponsor could be obtained, the small number of patients enrolled at the various investigative sites (i.e. no particular site enrolled a disproportionate number of patients), the timing of the studies relative to the publishing date of the financial disclosure rule, the due diligence by the applicant, and the low probability that these investigators actually had a financial interest as defined by the Agency in the financial disclosure rule, this reviewer does not consider financial interest to be a potential source of bias in the covered studies submitted with NDA 22-090.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review did not report issues that might affect efficacy or safety.

4.2 Clinical Microbiology

No issues to report.

4.3 Preclinical Pharmacology/Toxicology

The summary of pharmacology/toxicology states that there is a dose related, reversible tubular vacuolation seen in the kidney using rat and dog species repeat dose toxicity studies. This finding has also been observed with other gadolinium contrast agent and is not considered to be clinically important. A dose related, transient increase (~20 ms QTcF max) in QTc potential was seen with a NOAEL 0.025 mmol/kg that is roughly 0.5 x human dose. No cardiac safety signals were seen in the clinical trial data or reported in the foreign post marketing data.

4.4 Clinical Pharmacology

Clinical pharmacology review suggests that patients with combined renal and hepatic impairment be included in the observational phase 4 trial that is discussed under the post marketing commitment section (1.4 above).

Mechanism of Action

Gadoxetate disodium is a paramagnetic compound, and develops a magnetic moment when placed in a magnetic field. The magnetic moment produced by gadoxetate disodium results in a local magnetic field, yielding enhanced relaxation rates (shortening of relaxation times) of water protons in the vicinity of the paramagnetic agent, which leads to an increase in signal intensity (brightening) of blood and tissue. In magnetic resonance imaging (MRI), visualization of normal

and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) differences in proton density; 2) differences of the spin-lattice or longitudinal relaxation times (T1); and 3) differences in the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, Gadoxetate disodium decreases the T1 and T2 relaxation time in target tissue. At the recommended dose, the effect is observed with greatest sensitivity in T1-weighted MR sequences.

Pharmacodynamics

Studies performed do not raise concern regarding potential safety problems with QT prolongation, orthostatic events, or pharmacodynamics interactions.

Pharmacokinetics

Gadoxetate Disodium is a water soluble T1 contrast agent with high reflexivity (decreases the T1 relaxation time and increases the signal intensity), low protein binding (<11%), lack of biotransformation, active hepatic uptake, and dual excretion pathways of unmetabolized Gadoxetate Disodium into the bile and urine almost completely by 24 hours. The AUC (0-4 hours) accounts for about 90% of the AUC (0-infinity). The mean terminal half-life ranges from 1.1 – 1.6 hours, the total clearance ranges from 224 – 272 mL/min, and dose independent fecal and urinary excretion remains in 50:50 proportion over the dose range of 10 – 100 µmol/kg BW. Due to saturation of hepatic uptake at doses above 200 µmol/kg BW, the CLt (236 ml/min) and extent of fecal excretion decreases (36.8) and half-life (1.86 hours) shows a modest increase.

Special populations were studied that included hepatic impairment, renal impairment, coexistent renal and hepatic impairment, gender and age, and end stage renal disease (ESRD). The patients with ESRD revealed the most changes in pharmacokinetics.

- ESRD
 - The terminal half-life was longer
 - 20.4 hours compared to <3 hours in all other groups studied
 - The systemic exposure was higher
 - AUC was 5.6-fold higher in ESRF compared to the control group, and fecal excretion appeared to be increased.
 - Gadoxetate Disodium was found to be dialyzable
 - In a 3-hour dialysis session, started 1 hour after the dose, about 30 % of the Gadoxetate Disodium dose was removed by dialysis.
- Moderate renal impairment (GFR: 30 – 50 mL/min) and severe hepatic impairment (Child-Pugh category C):
 - The mean total clearance decreased by 28% and 33%
 - The mean total AUC increased by 48% and 60 %, respectively

- The terminal half-life increased slightly.
- Fecal excretion was lower in severe hepatic impairment (mean, 5.7% of dose), especially in patients with >3 mg/dL serum bilirubin (<0.5% of dose in the feces).
- A compensatory shift of urinary excretion was observed (mean urinary excretion of 61.3% in patients with severe hepatic impairment, and > 72% urinary excretion in patients with serum bilirubin >3 mg/dL).

Drug-drug interactions: Drug-drug interaction studies to evaluate the effect of Gadoxetate Disodium on PK of other drugs, and the effect of other drugs on PK of Gadoxetate Disodium were not undertaken because of Gadoxetate Disodium's non-chronic clinical application, lack of biotransformation (i.e. lack of involvement of cytochrome P450 enzymes), insignificant protein binding, and short half-life.

The effect of pretreatment with several commonly used drugs known to be excreted mainly via the hepatobiliary pathway on hepatic signal enhancement after Gadoxetate Disodium administration was investigated in a study in laboratory rats at 3 to 5 times the clinical doses. Only rifampicin, a known potent inhibitor of organic anion transporting polypeptides (OATP) significantly inhibited the hepatic enhancement. The drugs prednisolone, doxorubicin and propranolol hydrochloride which utilize the canalicular multispecific organic anion transporter (cMOAT) for their biliary excretion, slightly increased the hepatic signal enhancement, presumably by competitively inhibiting the biliary excretion of Gadoxetate Disodium.

Drug (generic name)	Dose [mg/kg]	Relative Liver Enhancement
Rifampicin, i.v.	40	Strong inhibition of contrast enhancement
Prednisolone, i.v.	40	Slightly longer lasting enhancement than volume control
Prednisolone, i.v.	100	Slightly longer lasting enhancement than volume control
Cisplatin, i.v.	2	Slightly longer lasting enhancement than volume control
Doxorubicin, i.v.	7	Slightly longer lasting enhancement than volume control
Propranolol hydrochloride, i.v.	4	Slightly longer lasting enhancement than volume control

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study No(s). Report No. Number of study centers Location(s)	Study period No. of patients planned / enrolled / treated	Study design and type of control	Study and control drugs: Dosage regimen Route of administration Duration of treatment	Study objectives
Phase 2 studies				

Clinical Review
 Cindy Welsh, MD
 NDA 22-090, Submission No. 000
 Gadoxetate Disodium Injection

Study no. 94051 Report no. AH34 10 centers Europe	July 1994 to Feb 1995 231/ 233/ 231	multi-center, double-blind, randomized, dose ranging, comparator controlled (pre contrast MRI)	Gadoxetate Disodium 3 doses: 12.5; 25.0; or 50 µmol / kg bw intravenous single dose	Diagnostic efficacy and safety of Gadoxetate Disodium at 3 doses (12.5; 25.0; and 50.0 µmol SH L 569 B) in patients with known focal liver lesions
Study no. 95058 Report no. AI94 7 centers Europe	June 1996 to Jan 1997 200 / 173 / 171	Multi-center, double-blind, randomized, dose ranging, placebo controlled	Gadoxetate Disodium 4 doses: 3.0, 6.0, 12.5, or 25 µmol/kg bw intravenous, single dose Placebo 0.9% saline, 5 mL intravenous single dose	Diagnostic efficacy and safety of Gadoxetate Disodium at 4 doses (3.0, 6.0, 12.5 and 25 µmol/kg BW) as compared to placebo (0.9% saline) in patients with known focal liver lesions
Study no. 95356 Report no. BA13 22 centers Japan	Sep 1995 to Aug 1997 180 / 186 / 186	Multi-center, open-label, randomized, single dose, consensus blinded reading, comparator controlled, (pre contrast MRI)	Gadoxetate Disodium 3 doses: 12.5; 25.0; 50.0 µmol / kg bw, intravenous single dose	To assess the optimal dose of Gadoxetate Disodium for liver MRI in patients with hepatic tumors by a random allocation, and to assess the safety and usefulness of Gadoxetate Disodium.
Patient PD and PK/PD Study Reports (Phase III)				
Study no. 14468 Report no. A04410 1 center USA	Oct. 2000 to May 2001 planned: 52 – 54 treated: 54 analyzed: 52 No dropouts	single center, open-label, parallel-group comparison one single dose	SH L569B: 25 µmol/kg body weight intravenous; one single injection	To determine the safety, pharmacokinetics, and pharmacodynamics (through MR imaging of the liver and related structures) of SH L569B in groups of volunteer patients with various levels of impaired hepatic function, impaired renal function, coexistent hepatic and renal impairment, and a control group of healthy volunteers matched for age, sex, weight, and smoking habits, a group of healthy elderly volunteers, and an aggregate group consisting of an equal number of healthy male and female volunteers.
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication Phase III studies				
Study nos.: Clinical study: 96129	Sep 1998 to Nov 1999 170/169/162	Clinical study: multi-center, open-label	SH L569B: 25 µmol/kg body weight	Detection of liver lesions Diagnostic efficacy and safety with regard to liver lesion

<p>Blinded reading: 98148</p> <p>Report no. A00518</p> <p>14 centers Europe</p>	<p>7 dropouts</p>	<p>one single dose</p> <p>comparator controlled (pre-contrast MRI, spiral CT)</p>	<p>intravenous, one single injection</p>	<p>detection of the MRI contrast agent SH L569B administered intravenously in one dose of 25 µmol/kg BW in adult patients with known/suspected liver lesions who were scheduled for surgery</p>
<p>Study no.</p> <p>Clinical study: 97160</p> <p>Blinded reading: 98146</p> <p>Report no. A03779</p> <p>12 centers USA</p>	<p>Sep. 1998 to Apr. 2000</p> <p>170/172/169</p> <p>3 dropouts</p>	<p>Clinical study: multi-center, open-label</p> <p>one single dose</p> <p>comparator controlled (pre-contrast MRI, spiral CT)</p>	<p>SH L569B: 25 µmol/kg body weight</p> <p>intravenous, one single injection</p>	<p>Detection of liver lesions</p> <p>Diagnostic efficacy and safety with regard to liver lesion detection of the MRI contrast agent SH L569B administered intravenously in one dose of 25 µmol/kg BW in adult patients with known/suspected liver lesions who were scheduled for surgery</p>
<p>Study nos.</p> <p>Clinical study: 12387</p> <p>Blinded reading: 303222</p> <p>Report no. A05742</p> <p>15 centers Europe</p>	<p>Apr. 2000 to Jun. 2001</p> <p>200/235/231</p> <p>4 dropouts</p>	<p>Clinical study: multi-center, open-label, <i>not</i> randomized</p> <p>one single dose</p> <p>comparator controlled (pre-contrast MRI, spiral CT)</p>	<p>SH L569B: 25 µmol/kg body weight</p> <p>intravenous, one single injection</p>	<p>Characterization of liver lesions</p> <p>Evaluation of the ability of SH L569B after a single intravenous injection to provide additional information for characterization of liver lesions and assessment of the safety of this MRI contrast agent in adult patients with known or suspected focal liver lesions.</p>
<p>Study nos.</p> <p>Clinical study: 14763</p> <p>Blinded reading: 303308</p> <p>Report no. A01908</p>	<p>Mar. 2000 to Feb. 2001</p> <p>250/240/235</p> <p>5 dropouts</p>	<p>Clinical study: multi-center, open-label, <i>not</i> randomized</p> <p>one single dose</p> <p>comparator controlled (pre-contrast MRI,</p>	<p>25 µmol/kg body weight</p> <p>intravenous, one single injection</p>	<p>Characterization of liver lesions</p> <p>Evaluation of the ability of SH L569B after a single intravenous injection to provide additional information for characterization of liver lesions and assessment of the safety of this MRI contrast agent in adult patients with known or suspected focal liver lesions.</p>

18 centers USA		spiral CT)		
Other phase 3 studies				
Study no. 300820	Aug 2001 to Mar 2003	Clinical study: Multicenter, open-label, Intra-individual, Single dose Blinded reading: Randomized sets of MR image scans; 3 independent blinded readers comparator controlled	Gadoxetate Disodium One single dose: 25 µmol/kg body weight Intravenous Single MR procedure, single injection	Gadoxetate Disodium after a single intravenous injection to provide additional information for detection and characterization of liver lesions and assessment of the safety of this MRIcontrast agent in adult patients with known or suspected malignant focal liver lesions.
Report no. A05868	180/ 178/ 178			
15 centers Japan				
Study no. 305654	Oct 2002 to Mar 2003	Clinical study: Multicenter, double-blind, randomized inter-individual comparative study, single dose Blinded reading: Randomized images; comparator controlled Reference: MultiHance®	Gadoxetate Disodium One single dose: 25 µmol/kg bw, intravenous, single MR procedure, single injection MultiHance® One single dose: 50 µmol/kg bw, Intravenous, single MR procedure, single injection	Evaluation of the non-inferiority of Gadoxetate Disodium after a single intravenous injection regarding the relative enhancement in normal liver parenchyma in T1- weighted images between pre- and post-contrast MRI images compared to MultiHance® in adult patients with known or suspected focal liver lesions.
Report no. A13241	220/ 295/ 295			
14 centers Europe				

5.2 Review Strategy

For evaluation of efficacy, this reviewer concentrated on the 4 pivotal phase 3 trials (Report numbers A00518, A03779, A05742, and A01908). Primarily, the focus of the review was evaluation of the primary efficacy endpoint including sensitivity and specificity of combined pre + post MRI vs. pre MRI in detection and characterization of liver lesions. Also considered were the post-hoc analyses requested by the Agency for this review and those performed for the EMEA review.

For evaluation of safety, this reviewer included the information from all of the trials which included ~1700 patients.

5.3 Discussion of Individual Studies

There were considerable modifications and discussions regarding the primary efficacy endpoint with the Agency during the formulation of the trial, and the evolution of the reviewing division's thinking regarding the stringency of the endpoint. The applicant has performed multiple post hoc secondary analyses evaluating the diagnostic performance of the product.

The primary clinical utility and primary endpoint of the trial was accuracy and was later changed to *sensitivity* based upon MRI (device alone) compared to MRI with test agent (contrast) or MRI (device alone) compared to MRI with and without test agent as compared to a truth standard.

The reviewing division recommended that the primary endpoints of the trial be *sensitivity and specificity* of test agent as compared to a truth standard in the following settings:

- Pre vs. post MRI (secondary endpoint but the applicant's original primary endpoint)
- Pre vs. pre + post MRI (primary endpoint)
- Pre MRI vs. spiral CT (deemed to be the current standard of care imaging modality for secondary endpoint)

The clinical trials were designed and performed to evaluate the primary efficacy endpoint as originally planned by the applicant (but not necessarily agreed to by the reviewing division). The NDA did not submit an imaging review charter for the blinded read portion of the trial. However, the NDA did include a blinded reader protocol in which the image acquisition and batch reads were prespecified and detailed. Specifically, there were no prespecified definitions of characterization or classification of the lesions. The characterization and classification were performed by each reader based upon general imaging descriptions of MRI lesions. Adjudication was not performed as the end point did not include measurement of lesion response. The protocol and statistical analysis plan did not specifically state what constitutes a 'win' although they imply that a 'win' is compatible when 2 of 3 readers are able to detect and characterize the lesions more often with the post MRI (either alone or combined with the pre MRI) as evaluated in a blinded read.

Study Design

The applicant sought indications for both the detection and characterization of liver lesions. To accomplish this goal, the applicant performed two identical phase 3 trials (one in the U.S. and the other in the E.U.) for each indication that included independent blinded reads to determine the primary efficacy endpoint.

Detection studies

	Detection Study A03779 US	Detection Study A00518 EU
Design	Phase 3 3 independent blinded readers for each study (6 total)	

6017 A01908	Male	54	Caucasian	USA	follow up 68-76 hrs	new left bundle branch block
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Patient 3017: ECG abnormal for bradycardia at baseline but worsened at 24 hours post-injection. The dose of the patient's baseline medication (metoprolol) was reduced. She had a full recovery.

Patient 3020: ECG was normal pre-injection and the patient developed first degree AV block at 2-4 hours that was continuing at the end of the trial.

Patient 6016: ventricular extra-systoles seen both pre and post-injection.

Patient 6017: The patient had a normal ECG at baseline up to 72 hours post-injection when he developed a left bundle branch block. There were associated increases in the QRS and QT interval and in the QTc values (from pre-contrast values of 97, 378, and 444 ms to 128, 403, and 482 ms at 72 hours post-injection, respectively). The bundle branch block was continuing at the end of the study. Therapeutic measures or other actions were not taken.

Overall, no ECG safety signals were seen in the phase 2/3 patients.

Additional analyses performed stratified by QT interval showed no difference.

Special Safety Studies

By creatinine level

Three subgroups classified into pre-injection creatinine level within normal range, ≤ 265.2 $\mu\text{mol/L}$ ($=3.0$ mg/dL) and > 265.2 $\mu\text{mol/L}$ were analyzed. Nine patients with creatinine level ≥ 265.2 $\mu\text{mol/L}$ were observed, including 6 patients with terminal renal impairment. The mean and median values of creatinine and BUN showed a large standard deviation and were lower at 2-4, 20-28 and 68-74 hrs post-injection than baseline. A similar stratified analysis was performed in the Japanese Phase II and Phase III studies. No significant difference was observed in the Phase II Study no. 95356 (follow up period 3 days). In the Phase III Study no. 300820, follow up period of three days, there was no patient in whom pre-injection creatinine level exceeded 3.0 mg/dL, and only 8 patients showed creatinine levels above the normal range but no more than 3.0 mg/dL. In these patients, no post-injection change was observed in either creatinine or BUN.

By liver function

Abnormal liver function was defined as baseline values of either AST/GOT, ALT/GPT or γ -GTP being two times higher than the upper limit of the reference range, or total bilirubin being 1.5 mg/dL or higher. The values were analyzed in subgroups with abnormal and normal liver function. No results suggesting post-injection changes were observed in subgroups of abnormal liver function. Only differences in the baseline values were observed between patients with abnormal and normal liver function subgroups.

Immunogenicity

The safety documents were searched for the terms antigen, antibody, immunogen, immunogenic, and immunogenicity. No results were found.

7.5 Other Safety Explorations

Drug-Demographic Interactions

The demographics of the trials were reflective of the demographics of the country in which the trial was performed. Therefore, the majority of the patients enrolled in these studies were Caucasian except for studies performed in Asian in which the patient population was predominantly Asian. Evaluation of the safety data by demographics revealed no safety signals although it is hard to draw any conclusions for the races with low representation in the trials.

Drug-Disease Interactions

Analyses were performed to assess the following:

By presence or absence of liver cirrhosis

No results suggesting post-injection changes were observed in the subgroup of patients with cirrhosis. Only differences in baseline values were observed between the subgroups.

By Child-Pugh Score

Regarding liver cirrhosis, classification into subgroups of unknown, A, B, and C were done according to Child-Pugh Score. No results suggesting that different post-injection changes between the Child's Score A and Score B subgroups were observed. Only differences in the pre-injection values were observed between them.

Drug-Drug Interactions

Preclinical information suggests that drugs that utilize the organic anion transport polypeptides, such as rifamycin, may interfere with the elimination of the drug. This is reflected in the labeling.

Analyses were performed to assess concomitant anticonvulsive and anti-arrhythmic medication:

By presence or absence of concomitant anticonvulsive medication

Fifteen patients taking concomitant anticonvulsive medication were included. In the subgroup analysis by use of the concomitant drug, no specific trends were observed in the subgroup taking concomitant anticonvulsive.

By presence or absence of concomitant anti-arrhythmic medication

There were 265 patients taking concomitant anti-arrhythmic medication included in the review. In the subgroup analysis by use of the concomitant drug, no specific trends were observed in the subgroup taking concomitant anti-arrhythmics.

7.6 Additional Safety Explorations

Human Carcinogenicity

The results of the genotoxicity studies performed in vivo and in vitro did not reveal any evidence for a mutagenic potential of Gd-EOB-DTPA. No carcinogenicity study of Gd-EOB-DTPA was performed because Gd-EOB-DTPA will only be administered once to humans for diagnostic purposes.

Human Reproduction and Pregnancy Data

There is no available information on drug exposure in pregnant women including inadvertent exposure during the drug development program or in the post-marketing data. Published data show that other gadolinium based contrast agents cross the placenta and result in fetal exposure.

Preclinical data:

Embryotoxicity occurred in pregnant rabbits that received daily Gadoxetate disodium at 26 times the recommended human dose (mmol/m² basis), and in pregnant rats at doses 3.2 times the human dose (mmol/m² basis). Animal reproductive and developmental toxicity studies were done in rats and rabbits. Gadoxetate disodium was not teratogenic when given intravenously during organogenesis to pregnant rats at doses up to 3.2 times the recommended single human dose (mmol/m² basis); however, an increase in pre-implantation loss was noted. Compared to untreated controls, rates of post-implantation loss and absorption increased and litter size decreased when pregnant rabbits received Gadoxetate disodium at doses 26 times the recommended human single dose (mmol/m² basis).

It is not known whether Gadoxetate Disodium is excreted in human milk.

Pediatrics and Effect on Growth

There is no data regarding the effect Gadoxetate Disodium may have on growth of pediatric patients as no studies that enrolled children (<18 years old) were performed.

Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose:

The maximum dosage studied in clinical trials was 500 µg/kg (N = 6 males + 4 females). Adverse events were recorded (2 nausea, 1 chest pain), but no new undesirable effects were observed in these patients.

The PSUR of May 2007 included the following report: A 40 year old patient (#GB-2006-040231) received a higher dose of Gadoxetate Disodium (20 ml) than intended as well as for the incorrect indication (brain and cervical spine imaging). No adverse reaction was observed immediately or later in the day. The sponsor was contacted via email regarding follow up greater than 1 day. The sponsor replied that no follow up was received.

Gadoxetate Disodium can be removed by dialysis.

Drug abuse potential, withdrawal and rebound:

No reported cases of withdrawal phenomena and/or abuse have been reported. This drug is a diagnostic agent with single dose indication. It is marketed to the diagnostic radiology physician population.

7.7 Additional Submissions

PSUR was submitted in November 2007. No safety signals were noted. The sponsor is modifying their proposed labeling to incorporate the class action changes recently enacted for the gadolinium based contrast agents currently on the market as well as submitting a post marketing commitment study to assess the risk of NSF.

8 Postmarketing Experience

Post marketing reports have been submitted. Tachycardia and restlessness were added to the European labeling based on global experience with the drug product. There have been no limitations to marketing due to safety issues.

During the reporting period 26 March 2004 – 31 March 2007:

- 12 spontaneous reports of adverse drug reactions
 - 3 serious – see tabulation below
 - 2 unlisted (tachyarrhythmia [a known (<1%) AE to gadolinium containing contrast agents: Magnevist, Optimark, Omniscan, and Multihance] and angina pectoris/acute coronary syndrome).
Note that tachycardia and restlessness were added to the EU label after initial approval.
 - 9 non-serious
 - no fatal case reported

- no cases of nephrogenic systemic fibrosis have been reported including the most recent post-marketing PSUR submitted November 2007.

During the post-marketing reporting period 26 March 2007 – 30 September 2007:

- 1 ongoing phase 3 registration trial in China
- No cases of NSF reported globally.
- Foreign marketing experience
 - 2 non-serious reports: 1 injection site pain and 1 diarrhea.
 - 1 serious report (MedWatch): transient global amnesia, amnesic aphasia, and confusion occurred 15 minutes post-injection of 10 ml of Gadoxetate Disodium that required hospitalization (4 days). The symptoms resolved after 24 hours without treatment. The 62 year old male patient had a history of hepatic neoplasm and food allergy.

Reviewer's comment: Injection site pain is currently labeled. Diarrhea and the serious report mentioned above are not labeled reactions. Based on the review of the case report form for this serious report alone, this reviewer would not recommend adding these reactions to the label.

Final post-marketing safety update filed November 2007 to the application: No additional new information to add to the safety profile.

9 Appendices

9.1 Literature Review/References

A Medline search for safety and exposure to Gadoxetate Disodium in pediatric population was performed. No important new information was identified.

9.2 Labeling Recommendations

Please see printed label for agreed-upon final version of the document.

9.3 Advisory Committee Meeting

Not indicated.

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/s/

Cynthia Welsh
4/25/2008 11:01:12 AM
MEDICAL OFFICER

Libero Marzella
4/25/2008 11:36:35 AM
MEDICAL OFFICER

From : Ramzi Dagher, MD
DDOP consult reviewer

To : DMIHP
Cynthia Welsh, MD
Medical Reviewer

Tiffany Brown, M.P.H
Regulatory Project Manager

Subject : Primovist (NDA # 22090) consult from DMIHP
regarding pediatric development

Background

According to the cover letter included in the NDA 22-090 filing dated June 29, 2007, "...Primovist® Injection is an aqueous solution containing the new gadolinium chelate gadolinium-EOB-DTPA. Chemically, a lipophilic moiety was added to Gd-DTPA (Magnevist®) resulting in a weak protein binding and enabling PRIMOVIST to enter the hepatocytes via membrane bound carriers. This unique property leads to an enhancement of the normal liver tissue during the hepatocyte phase, improving the detection of liver lesions via the increased signal intensity difference between normal liver parenchyma and liver lesion. Hence, PRIMOVIST combines the features of an extracellular contrast agent and a hepatocyte-specific agent...Different from other gadolinium based agents, this agent has a dual elimination pathway via the renal and the hepatobiliary system"

During the review process, DMIHP consulted PeRC regarding the acceptability of a pediatric waiver. PeRC did not agree with granting a pediatric waiver. DDOP is now being consulted regarding the PeRC position.

DDOP Reviewer Comments

The annual incidence of liver tumors in children and adolescents in the United States is estimated at 100 to 150 new cases. Furthermore, imaging is an important component of the diagnosis and staging of these tumors. One of the most important prognostic factors in outcome is resectability, and imaging plays an important role in determination of resectability either upfront or after cytoreductive therapy.

The two most common histologic subtypes are hepatoblastoma and hepatocellular carcinoma. Hepatoblastoma tends to occur in younger children, with a mean age at diagnosis of 19 months and an incidence of only 5% after the age of 4. Hepatocellular carcinoma occurs primarily after the age of 10 with hepatitis B as the clearest pathogenetic factor. Outside of the United States, the incidence of hepatocellular carcinoma in older children and adolescents is much higher than in the United States, with an annual incidence in Asia estimated to be 10 times that in the US.

Reviewer Recommendations

Based on these considerations and the purported effect of this contrast agent in optimizing MRI imaging of the liver, DMIHP is encouraged to grant a deferral as opposed to a waiver of pediatric studies. The possibility of conducting one or more studies to explore relationships between dose, PK, and MRI imaging characteristics in children with hepatoblastoma and hepatocellular carcinoma should be discussed with the NDA applicant. These studies could include international sites in order to increase the enrollment of patients with hepatocellular carcinoma. The design of these studies should be discussed internally with the clinical pharmacology review team.

References

1. Tomlinson GE and Finegold MJ. Chapter 29 Tumors of the Liver in Principles and Practice of Pediatric Oncology. 4th Edition. Pizzo PA and Poplack DG editors. Lippincott Williams and Wilkins 2002.
2. Czauderna P, Otte JB, Aronson DC, et al; Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Guidelines for surgical treatment of hepatoblastoma in the modern era--recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Eur J Cancer 41:1031-1036, 2005.
3. Czauderna P, Mackinlay G, Perilongo G et al. Hepatocellular Carcinoma in Children: Results of the First Prospective Study of the International Society of Pediatric Oncology Group. J Clin Oncol 20:2798-2804, 2002.

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/s/

Ramzi Dagher
4/9/2008 09:19:00 AM
MEDICAL OFFICER

Division of Medical Imaging and Hematology Products
NDA 22090, Serial No. 000
November 7, 2007

The following letter was sent to Dr. Robert Mattrey. Dr. Mattrey agreed to advise the division as a Special Government Employee (SGE) on the efficacy and safety of this product.

Dear Dr. Mattrey,

Thank you for agreeing to provide advice on the New Drug Application (NDA) to the Division of Medical Imaging and Hematology Products at the FDA. Enclosed please find the Summaries of Clinical Efficacy and Safety for the NDA. I will also include the Clinical Overview for background material to assist in your review.

Please focus your review on the efficacy of this drug with respect to the proposed indications of detection of liver lesions (part 1 - consists of 2 identical studies performed; one in the US and one in the EU) and then the subsequent classification and characterization (part 2 - consists of 2 identical studies performed; one in the US and one in the EU) of the detected lesions. Please note that the patient populations and the standard of truth differ between the studies evaluating the two proposed indications. You will also note that the number of cases where there is a difference in detection is small. Please comment on the clinical importance of this difference. Also, please comment on the adequacy of the image acquisition protocols for the purpose of optimal visualization of the liver lesions.

Please provide a brief summary of your findings and recommendations by December 14, 2007.

Please note that this application is currently under review by the agency and that the information contained in this email and the attachments are confidential and not to be disclosed.

Sincerely,
Cindy

Cindy Welsh, MD
Medical Officer
Division of Medical Imaging and Hematology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301.796.2168

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/s/

Cynthia Welsh
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Libero Marzella
11/8/2007 07:23:47 PM
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