Safety of Gadobenate Dimeglumine (MultiHance)

Summary of Findings From Clinical Studies and Postmarketing Surveillance

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**Objectives:** Prospective studies and retrospective analyses were undertaken to evaluate the clinical safety of gadobenate dimeglumine (MultiHance) and to assess tolerability in special populations.

**Materials and Methods:** A total of 3092 subjects received MultiHance in 79 clinical trials. Data from comparisons with other contrast agents and studies in children, subjects with hepatic or renal impairment, or subjects with coronary artery disease were reviewed. Postmarketing safety surveillance data after more than 1.5 million applications were also evaluated.

**Results:** In total, 413 of 2982 (14%) adult subjects receiving MultiHance reported at least one adverse event (AE) definitely or potentially related to MultiHance, an incidence that was similar to that observed with placebo (21/127, 17%) or active controls (59/723, 8%). In cross-over studies, 23 of 287 (8%) subjects receiving MultiHance experienced AE compared with 25 of 295 (9%) receiving gadopentetate dimeglumine (Magnevist). No increased AE rate was observed in children and no worsening of renal or liver function was observed in subjects with hepatic or renal impairment. No detrimental effect on cardiac electrophysiology could be observed from a retrospective analysis of ECG parameters in more than 1000 patients and healthy volunteers. The AE reporting rate from postmarketing safety surveillance of MultiHance was 0.05%. Serious AEs were rarely reported and included dyspnea, nausea, urticaria, hypotension, and anaphylactoid reactions.

**Conclusions:** MultiHance appears to be well tolerated in adults and children and in subjects with impaired liver or kidney function or coronary artery disease. In controlled trials, MultiHance demonstrated a similar safety profile to that of Magnevist.

**Key Words:** MRI contrast media, gadolinium, adverse effects, comparative studies

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To date, 8 gadolinium-based magnetic resonance imaging (MRI) contrast agents have been approved for clinical use in 1 or more countries of the world, 5 of which are approved for use in the United States. The first of these agents, Magnevist (gadopentetate dimeglumine [Gd-DTPA], Berlex Inc., Montville, NJ) received U.S. Food & Drug Administration (FDA) approval in 1988 and the most recent, MultiHance (gadobenate dimeglumine [Gd-BOPTA], Bracco Diagnostics Inc., Princeton, NJ), in 2004. Most gadolinium-based agents are similar with regard to their physical properties, mode of action, and general safety profiles. However, MultiHance differs from the others in possessing markedly higher r1 and r2 relaxivity values than other available gadolinium-based agents. Importantly, these properties have been shown to translate into a greater contrast enhancing effect in vivo. MultiHance also undergoes limited uptake by normally functioning hepatocytes and biliary excretion, resulting in increased delayed liver-lesion contrast. Although MultiHance has been reported to offer potential efficacy advantages over other gadolinium-based contrast agents (eg, higher signal intensity changes and liver-specific contrast enhancement) if it is to be viewed as an improved or advanced agent, it also must have a comparable safety profile to that of the other approved gadolinium agents.

Previously, Kirchin et al evaluated the safety of MultiHance in clinical studies conducted in the United States and Europe between 1990 and 2000. Since then, a number of studies have been conducted in which MultiHance was shown to compare favorably with other gadolinium-based agents, including Magnevist and Dotarem (gadoterate meglumine [Gd-DOTA], Guerbet S.A., Paris, France), for MRI of the central nervous system (CNS), vasculature, breast, and liver. To critically evaluate the safety of MultiHance, we reviewed updated safety clinical data, including data from recently conducted studies comparing MultiHance with other widely used gadolinium-based agents. In addition, the safety of MultiHance in special populations, including children with
CNS disease, and patients with coronary artery disease (CAD), kidney, and liver failure were reviewed. Finally, postmarketing surveillance data were reviewed for safety findings associated with the routine clinical use of MultiHance after more than 1.5 million applications.

**MATERIALS AND METHODS**

**Subject Exposure and Safety Monitoring**

A total of 3092 subjects (2863 adult patients, 119 healthy volunteers, and 110 pediatric subjects) received MultiHance (gadobenate dimeglumine injection, Bracco Diagnostics Inc., Princeton, NJ) in 79 clinical trials completed by August 2004. These trials were conducted in accordance with Good Clinical Practice (GCP) in the United States, Europe, and China. All protocols were reviewed by the study centers' respective institutional review board or ethics committee, and all enrolled subjects provided written informed consent prior to participation in the studies.

Controlled studies were designed as parallel-group or crossover comparisons. In all controlled studies, subjects were either randomized to the treatment group (MultiHance or control agent), or if both agents were given to the same subjects (crossover studies), the order of administration was fully randomized. A total of 850 subjects (758 patients and 92 volunteers) received either placebo control (saline, \( n = 127 \)) or an active control (\( n = 723 \)) in controlled studies. Active controls included Magnevist (Gd-DTPA injection, Berlex Laboratories, Wayne, NJ; \( n = 561 \)), Omniscan (gadodiamide injection, GE Healthcare, Princeton, NJ; \( n = 134 \)), or Dotarem (gadoterate dimeglumine injection, Guerbet Laboratories, Paris, France; \( n = 28 \)). In parallel-group studies, adult study subjects received either MultiHance (\( n = 799 \)) or a control agent (\( n = 391 \)), either Magnevist (\( n = 177 \)), Omniscan (\( n = 134 \)), or saline (\( n = 80 \)). An additional parallel-group study comparing MultiHance (\( n = 85 \)) with Magnevist (\( n = 89 \)) was conducted in children younger than 18 years of age undergoing MRI of the CNS. A further 377 adult patients or volunteers were enrolled in intraindividual crossover comparison studies in which subjects received both MultiHance and another gadolinium agent or a saline placebo in randomized order. Subjects in these studies received MultiHance (\( n = 362 \)) and either Magnevist (\( n = 295 \)), Dotarem (\( n = 28 \)), or placebo (\( n = 47 \)).

The mean administered dose of MultiHance was 0.113 mmol/kg. Most adult subjects (\( n = 2020 \)) and all pediatric subjects received a single bolus injection (2 mL/s) of MultiHance at a dose of 0.1 mmol/kg body weight or less. A further 675 subjects received a dose between 0.1 and 0.2 mmol/kg. The remaining subjects were given doses of MultiHance between 0.2 and 0.4 mmol/kg. Specific safety monitoring varied by study, but the safety and tolerability of MultiHance were generally evaluated by means of the following: complete physical examination on screening and at 24 hours after study agent injection; continuous patient monitoring for adverse events (AEs) after a minimum of follow-up in some studies of up to 96 hours; recording of vital signs (blood pressure and heart rate) preinjection and at different time-points for at least 24 hours postdose; 12-lead electrocardiographic (ECG) controls on screening as well as at different time-points up to 24 hours after dose (with a maximum follow-up of up to 72 to 96 hours); and clinical laboratory investigations (hematology, blood chemistry, and urinalysis) conducted before dose and at 24 hours after injection.

All AEs, defined as unintended and unfavorable signs, symptoms, or diseases temporally associated with the administration of MultiHance or control agent, were collected and analyzed. AEs were graded for intensity (mild: event not resulting in disability/incapacity, which resolves without treatment; moderate: event not resulting in disability/incapacity, which requires treatment; severe: event resulting in temporary and/or mild disability/incapacity, which requires treatment) and for relationship to the study agent (definite, probable, possible, doubtful, unknown, or unrelated). Serious AEs, defined as any untoward medical occurrence during the study period that was life-threatening, required hospitalization or prolonged existing hospitalization, or resulted in persistent or significant disability/incapacity or death, were collected and analyzed for any potential relationship to drug administration.

AE incidence rates were calculated for MultiHance and for the various control groups by dividing the number of subjects reporting AE by the number of patients exposed. Statistical analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC). \( \chi^2 \) analysis was used to test for significant differences (\( P < 0.05 \)) in the rate of AE after MultiHance and control groups.

**Comparative Studies With Magnevist**

Most of the controlled studies with MultiHance used Magnevist as the validated comparator. A total of 924 patients were enrolled in trials comparing these 2 agents. Four studies involving 625 subjects were designed as parallel-group comparisons of the 2 agents. In these studies, patients received either MultiHance (\( n = 359 \)) or Magnevist (\( n = 266 \)) and were monitored for clinical, instrumental, or laboratory AEs for 24 hours after the administration of the contrast agents. Six crossover, intraindividual studies involving 299 subjects also were performed. In these studies, subjects received both agents in randomized order with a washout interval of at least 24 hours between the 2 injections. Eight patients in crossover studies terminated the study after the administration of Magnevist because of extravasation of the contrast agent during the first examination, withdrawal of consent for personal reasons, or withdrawal of consent because of an adverse event during the first examination. Patients were monitored for AEs for 24 hours after the administration of each study agent. AE rates were calculated for both parallel-group and crossover comparisons as number of patients reporting one or more AE over the total number of patients dosed. We undertook \( \chi^2 \) analysis to test for significant differences in the rate of AE between study groups.

**Safety Assessment in Children**

Two clinical studies were conducted to assess the pharmacodynamics, safety and efficacy of MultiHance in children aged 2 months to 18 years of age. A pharmacokinetic study was performed in 25 healthy male or female subjects between the
ages of 2 to <16 years old.20 In this study, all 25 subjects (14 boys, 11 girls) received a single intravenous dose of 0.1 mmol/kg MultiHance and were monitored for at least 24 hours after dosing. Mean age and weight for the 16 children (ages 2 to <12 years of age) were 7.7 ± 2.2 years and 27.9 ± 9.5 kg, respectively, and for the 9 adolescents (ages 12 to <16 years of age) were 13.4 ± 1.0 years and 55.6 ± 10.3 kg, respectively. Safety was assessed by recording predose and postdose vital signs, laboratory results (hematology, blood chemistry, and urinalysis), electrocardiograms, physical examinations, and the incidence of AE.

In a separate trial, 174 children ages 6 months to 17 years with suspected CNS disease were assigned randomly to receive a 0.1 mmol/kg dose of either MultiHance or Magnevist at an injection rates ranging from 10 mL/min to bolus (2 mL/s or greater).7,19 Safety was assessed by changes from baseline in vital signs and laboratory findings together with the incidence of AE and tabulated by study agent. Eighty-five pediatric patients received MultiHance (54% men, 46% women) and 89 patients received Magnevist (48% men, 52% women). The 2 study agent groups were comparable with respect to medical history at baseline and concomitant medications. Ages ranged from 4 days to 17 years of age in the MultiHance group (mean age, 6.8 years) and from 7 months to 17 years in the Magnevist group (mean age, 4.7 years).

Renal Safety Assessment

The safety and pharmacokinetics of MultiHance were assessed in 32 patients (20 MultiHance, 12 placebo) with renal impairment (urine creatinine clearance: >30 mL/min and ≤60 mL/min; ≥10 mL/min and ≤30 mL/min) and in a separate study conducted in 17 patients (11 MultiHance, 6 placebo) requiring renal dialysis.21,22 In these studies, MultiHance or a saline placebo was administered as a single intravenous dose of 0.3 mmol/kg (renally impaired patients) or 0.2 mmol/kg (dialysis patients). Renal function and clearance were measured, and safety was determined by predose and postdose vital signs, laboratory results (hematology, blood chemistry, urinalysis, and iron metabolism), electrocardiograms, physical examinations, and by the incidence of adverse events monitored for up to 72 hours after drug administration.

Subsequently, a retrospective analysis was conducted in 2121 patients with serial measurements of serum creatine (Scr) values. Renal function was determined on the basis of creatinine clearance (CrCl) values, which were calculated from the predose serum creatinine concentration (the last predose value was taken, in case several values were obtained), using the formula of Cockcroft and Gault.23 Subgroup analyses were performed based on the following categories: no renal impairment (CrCl ≥ 80 mL/min); mild renal impairment (50 mL/min ≤ CrCl < 80 mL/min); moderate renal impairment (30 mL/min ≤ CrCl < 50 mL/min); and severe renal impairment (CrCl < 30 mL/min). In these retrospective safety analyses, the renal safety of MultiHance in adults or children was assessed based on examination of reported AE and changes in laboratory data, including after-dose Scr measurements.

Hepatic Safety Assessment

A small percentage of the injected dose of MultiHance (1–4%) is excreted into the bile.16,17 To assess possible safety implications of this biliary excretion, a prospective study was performed in subjects with impaired liver function and a series of retrospective safety analyses were performed on the clinical trial database to examine the predose to postdose shifts in liver enzymes and bilirubin (total and conjugated) in adult patients with liver disease.

In the prospective study, the safety and clearance of a single bolus injection of 0.1 mmol/kg MultiHance was assessed in 11 subjects with stable chronic hepatic impairment; an additional 5 subjects with hepatic impairment received a saline placebo.24 Safety was determined by predose and postdose vital signs, laboratory results (hematology, blood chemistry, urinalysis), iron metabolism, electrocardiogram, physical examinations, and the incidence of AE from drug administration to 3 days after injection. Safety and pharmacokinetic data were analyzed and compared between the MultiHance and placebo groups. The overall incidence of AE liver impairment group was calculated and compared with that of the adult liver study population as a whole. In one controlled trial, 222 adult patients with liver disease were studied after injection of MultiHance (n = 179) or a saline placebo (n = 43).10 A total of 1252 patients were studied after MultiHance in liver imaging or safety studies. A series of retrospective safety analyses were performed on the liver imaging/liver impairment subset. Adverse event rates were calculated for this subgroup and compared with rates in the adult population as a whole. Predose and postdose (24 hour) liver enzymes and bilirubin (total and direct) data were pooled and analyzed for marked deviation from baseline values in the adult population as a whole and in adult patients with cirrhosis, with subset analysis by the severity of the disease. Cirrhosis was defined as “Mild” if both serum albumin > 3.5 g/dL and serum bilirubin < 2 mg/dL, or serum albumin > 3.5 g/dL or serum bilirubin < 2 mg/dL if only 1 parameter was measured; “Moderate” if either serum albumin 2.8 to 3.5 g/dL or serum bilirubin 2 to 3 mg/dL and neither met the criteria for severe; or “Severe” if either serum albumin < 2.8 g/dL or serum bilirubin > 3 mg/dL. Liver function tests performed in the pediatric population (n = 110) also were review for any indication of deterioration of hepatic function following administration of MultiHance.

Cardiac Safety Assessment

Adverse event rates were calculated for the subgroup of patients (n = 186) enrolled in cardiac imaging studies using MultiHance at doses from 0.05 to 0.3 mmol/kg and compared with rates in the adult population as a whole. To evaluate the potential effects of MultiHance on electrophysiological parameters, intermittent 12-lead ECG data in 1045 patients enrolled in clinical trials with MultiHance were analyzed retrospectively. Shifts from normal range and any changes of potential clinical importance from predose (>32 milliseconds for PR intervals; >16 milliseconds for QRS intervals, and >60 milliseconds for QT [or QTc] intervals) were evaluated. Incidental AE involving ventricular arrhythmias recorded
RESULTS

Overall AEs

A total of 531 (18%) of the 2982 adult subjects who received MultiHance experienced one or more AE. Of these, 415 (14%) reported AE that were considered of definite, probable, possible, doubtful, or unknown relationship to MultiHance. The majority of patients reported AE that were mild (388/531, 73%) or moderate (91/531, 17%) in intensity and rapidly self-resolving. The incidence and type of AE after MultiHance were similar to that observed with placebo (35/127, 28%) or active controls (91/723, 13%; Table 1). The most frequently reported AEs considered to be potentially related to MultiHance or controls were headache (2% with MultiHance and controls), nausea (2% with MultiHance, 1% with controls), injection site reaction (1% with MultiHance, 1.0% with controls), and flushing (1% with MultiHance, 1% with controls). All other AE were reported with an incidence of <1% for the adult subjects given MultiHance.

Most subjects (n = 2020) received a dose of 0.1 mmol/kg or less; the AE rate in this group (16%) was similar to that in the overall exposure population (18%). A reduced AE incidence was noted in patients older than 65 years of age (14%) versus those 18 to 65 years of age (19%); however, no trends in AE were apparent on the basis of sex, weight, or race.

Comparative Studies With Magnevist

In parallel-group studies, AEs were reported in 11% (39/359) of subjects after MultiHance and 8% (21/266) after

| TABLE 1. Overall Incidence and Most Frequent AEs With MultiHance and Control Agents |
|----------------------------------|----------------------------------|------------------|
|                                  | All AE                           | Related AE*      |
| Subjects exposed                 | MultiHance, n (%)                | All Control, n (%)| Active Control, n (%)| Saline Control, n (%) | MultiHance, n (%) | All Control, n (%) | Active Control, n (%)| Saline Control, n (%) |
| No. AE                           | 2982†                            | 850              | 723†               | 127                 | 2982†            | 850              | 723†               | 127                 |
| No. subjects with AE             | 531 (18)                         | 126 (15)         | 91 (13)            | 35 (28)             | 413 (14)         | 80 (9)           | 59 (8)             | 21 (17)             |
| Intensity§                       | Mild                             | 388 (13)         | 74 (9)             | 41 (6)              | 33 (26)          | 317 (11)         | 52 (6)             | 31 (4)              | 21 (17)             |
|                                  | Moderate                         | 91 (3)           | 11 (1)             | 7 (<1)              | 4 (3)            | 55 (2)           | 6 (<1)             | 5 (<1)              | 1 (<1)              |
|                                  | Severe                           | 10 (<1)          | 1 (<1)             | 1 (<1)              | 0 (0)            | 4 (<1)           | 1 (<1)             | 1 (<1)              | 0 (0)               |
|                                  | Not reported                     | 42 (1)           | 2 (<1)             | 2 (<1)              | 0 (0)            | 37 (1)           | 1 (<1)             | 1 (<1)              | 0 (0)               |
|                                  | Serious AE                       | 15 (<1)          | 3 (<1)             | 3 (<1)              | 0 (0)            | 5 (<1)           | 1 (<1)             | 1 (<1)              | 0 (0)               |
| Most frequent AE                 | Headache                         | 67 (2)           | 21 (2)             | 15 (2)              | 6 (5)            | 49 (2)           | 14 (2)             | 10 (1)              | 4 (3)               |
|                                  | Nausea                           | 55 (2)           | 10 (1)             | 8 (1)               | 2 (2)            | 48 (2)           | 8 (1)              | 7 (1)               | 1 (<1)              |
|                                  | Injection site reaction          | 44 (1)           | 10 (1)             | 7 (1)               | 4 (3)            | 38 (1)           | 9 (1)              | 5 (1)               | 4 (3)               |
|                                  | Vasodilatation                   | 31 (1)           | 5 (<1)             | 5 (1)               | 0 (0)            | 31 (1)           | 5 (1)              | 5 (1)               | 0 (0)               |
|                                  | Taste paresthesia                | 25 (<1)          | 12 (1)             | 9 (1)               | 3 (2)            | 25 (1)           | 12 (1)             | 9 (1)               | 3 (2)               |
|                                  | Paresthesia                      | 23 (<1)          | 10 (1)             | 8 (1)               | 2 (2)            | 23 (1)           | 6 (1)              | 6 (1)               | 0 (0)               |
|                                  | Dizziness                        | 22 (<1)          | 8 (<1)             | 6 (1)               | 2 (2)            | 16 (<1)          | 5 (1)              | 5 (1)               | 0 (0)               |

*Includes AE with definite, probable, possible, doubtful, remote, unknown or missing relationship to the study agent.
†All adult subjects (patients and volunteers) given MultiHance.
‡Active control group includes adult and pediatric subjects given Magnevist (n = 561), Omniscan (n = 134), or Dotarem (n = 28).
§If more than one AE occurred, the maximum intensity was counted.
Magnevist (P = 0.21). In intraindividual crossover studies in which patients acted as their own controls, the AE rate was 8% (23/287) after MultiHance and 9% (25/295) after Magnevist (P = 0.84). Most AE were minor, transient, and self-limiting after either contrast agent. The type of AE reported were similar between agents, including headache, injection site reactions, mild rash, and nausea. The majority of subjects enrolled in crossover comparisons with Magnevist to date were studied in CNS trials (Table 2). In these studies, the AE rate was 8% (14/177) after MultiHance and 9% (16/183) after Magnevist (P = 0.77).

### Safety Assessment in Children

In the pharmacodynamic study of MultiHance in children aged 2 months to younger than 16 years, 4 mild AE were reported, all of which were considered possibly related to the administration of MultiHance injection. Two children (2/16, 13%) experienced 3 AE, whereas 1 adolescent subject (1/9, 11%) experienced 1 AE. No AE required treatment and all resolved without sequelae. No clinically meaningful findings for either age subgroup were noted for other safety parameters, and no clinically meaningful after-dose changes in laboratory values and vital signs were identified. The pharmacokinetic profile of MultiHance in this study was similar to that previously identified in adult subjects.

In the study conducted in 17 hemodialysis patients (11 MultiHance, 6 placebo), a total of 24 AE were reported for 14 of 17 patients: 11 patients receiving MultiHance (100%) experienced 19 AE, and 3 of 6 placebo patients (50%) experienced 5 AE (P = 0.003). Of these, 12 AEs in 7 subjects receiving MultiHance (7/11; 64%) and 2 AEs in the 6 subjects (2/6, 33%) receiving placebo were considered to be related to the study agent. All postdose AEs were mild to moderate in intensity, and all resolved without sequelae with the exception of one event for one MultiHance (abdominal pain caused by menstrual cramps) and 1 event for 1 placebo patient (abnormal electrocardiogram, possibly related to drug administration). These events were noted as still present at the patients’ last assessment. None of the AE in subjects receiving MultiHance was considered related to the study agent; however, 1 AE in the placebo group (taste perversion) was considered to be potentially related to the study agent. The relationship of another AE to placebo (nausea) was unknown. None clinically meaningful findings for either study agent group were noted for other safety parameters. As expected, renal elimination was slower in patients with more severe renal impairment. However, the overall extent of renal elimination was not affected by the subjects’ degree of renal impairment.

### Renal Safety Assessment

In the safety and pharmacokinetic study of MultiHance in 32 patients with renal impairment, 10 study subjects reported a total of 16 AE. Five subjects (5/20, 20%) in the MultiHance group experienced 9 AEs, and 5 subjects receiving placebo (5/12, 42%) experienced 7 AEs (P = 0.32; Table 3). All AEs reported in this study were mild to moderate in intensity, and none required treatment or resulted in sequelae. None of the AE in subjects receiving MultiHance was considered related to the study agent; however, 1 AE in the placebo group (taste perversion) was considered to be potentially related to the study agent. The relationship of another AE to placebo (nausea) was unknown. No clinically meaningful findings for either study agent group were noted for other safety parameters. As expected, renal elimination was slower in patients with more severe renal impairment. However, the overall extent of renal elimination was not affected by the subjects’ degree of renal impairment.

### TABLE 2. Overall Incidence of AEs in Intraintdividual Crossover Studies With MultiHance and Magnevist

<table>
<thead>
<tr>
<th>Population</th>
<th>Subjects (n)</th>
<th>Subjects With AE (n)</th>
<th>AE Incidence (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>287</td>
<td>23</td>
<td>8</td>
<td>0.84</td>
</tr>
<tr>
<td>MultiHance</td>
<td>295</td>
<td>25</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Magnevist</td>
<td>177</td>
<td>14</td>
<td>8</td>
<td>0.77</td>
</tr>
<tr>
<td>CNS Trials</td>
<td>183</td>
<td>16</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Liver trial</td>
<td></td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>MultiHance</td>
<td>42</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Magnevist</td>
<td>43</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>MRA trials</td>
<td></td>
<td></td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>MultiHance</td>
<td>68</td>
<td>8</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Magnevist</td>
<td>69</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

CNS, central nervous system; MRA, magnetic resonance angiography.

### TABLE 3. Incidence of AEs in Prospective Comparative Studies in Special Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>AE Incidence</th>
<th>Control Agent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with CNS disease</td>
<td>MultiHance</td>
<td>Control</td>
<td>P</td>
</tr>
<tr>
<td>11/85 (13)</td>
<td>13/89 (15)</td>
<td>Magnevist</td>
<td>0.75</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>5/20 (25)</td>
<td>5/12 (42)</td>
<td>0.32</td>
</tr>
<tr>
<td>Impaired liver function</td>
<td>1/11 (9)</td>
<td>2/5 (40)</td>
<td>0.14</td>
</tr>
<tr>
<td>Subjects with coronary artery disease</td>
<td>5/23 (22)</td>
<td>4/23 (17)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

CNS, central nervous system.
patients with adverse events was observed with increasing severity of renal impairment.

Overall, for renal function parameters (urea nitrogen and creatinine) there were no changes in the percentage of patients with values above or below the normal reference range that indicated any clinically meaningful trend over the postdose time points. The majority of patients had values that were within the normal range both at baseline and after dose. Less than 5% of patients showed changes that were within the normal range at baseline and outside the normal reference range at 24 hours. Urea nitrogen values (mg/dL) were available in 1195 subjects at 24 hours; decreases outside the normal range were recorded in 7 subjects (1%), whereas increases were noted in 26 subjects (2%). At 24 hours after dose, creatinine values (mg/dL) were available in 1781 subjects; serum decreases outside the normal range at 24 hours. Urea nitrogen values (mg/dL) were available in 1195 subjects at 24 hours; decreases outside the normal range were recorded in 7 subjects (1%), whereas increases were noted in 26 subjects (2%). At 24 hours after dose, creatinine values (mg/dL) were available in 1781 subjects; serum decreases outside the normal range were recorded in 26 subjects (2%). No significant trends of increased incidence of renal or nonrenal untoward effects were identified when renal safety data were examined based on increasing severity of renal impairment.

Hepatic Safety Assessment

In the prospective study performed in 16 subjects with stable chronic hepatic impairment, 11 subjects received a single bolus injection of 0.1 mmol/kg MultiHance whereas 5 received an injection of a saline placebo. In this pharmaco-dynamic study, dose and/or body weight normalized pharmacokinetic parameters were similar to the range seen in previous studies in healthy subjects, demonstrating that MultiHance pharmacokinetics were minimally affected by hepatic impairment.24 A total of 4 AE were reported for 3 patients in the study: 1 subject receiving MultiHance (1/11, 9%) experienced constipation, whereas 2 subjects receiving placebo (2/5, 40%) experienced 3 AE (abdominal pain, am-blyopia, and injection site reaction; \( P = 0.14 \), Table 3). All of the AE were mild in intensity and none of the AE was related to any sign of liver toxicity/impairment. The one AE in a subject receiving MultiHance, and 2 of the AE (abdominal pain, injection site reaction) in the placebo group were considered to be possibly related to the study agent. Of note, the overall incidence of AE after MultiHance in the liver impairment group (9%) was lower than that seen in the adult population as a whole (18%; \( P = 0.45 \)). No other clinically meaningful findings for either study agent group were noted for other safety parameters, including physical examination, vital signs, and laboratory (hematology, serum chemistry, urinalysis, iron metabolism) results.

Analyses on the liver imaging/liver impairment group showed that the rate of AE in this group (207/1252, 17%) was comparable with the rate in the adult subject population as a whole (18%). The incidence of AE was higher in the one controlled trial in adult patients with liver disease, although the AE rate was similar in patients who received MultiHance (79/179, 44%) and in patients who received placebo (19/43, 44%; \( P = 0.99 \)). The most frequently recorded AE were similar between the liver study population and the overall population (headache 2% vs. 2% overall, nausea 2% vs. 2% overall, injection site reaction 1% vs. 2% overall). In patients with cirrhosis who received MultiHance, the overall incidence of AE was similar to that in patients without cirrhosis who received MultiHance in liver studies (all AE, 17% vs. 16%). No liver function test abnormalities (ie, increased bilirubin or liver enzymes) were reported as AE in patients with cirrhosis.

The majority of patients had hepatic laboratory values within the normal range both at baseline and postdose. Shifts in laboratory values after MultiHance were similar to those for placebo-treated patients in the liver imaging/impairment population. For the majority of parameters, <5% of the patients had values that were within the normal range at baseline and outside the normal range at 3, 24, or 72 hours postdose. The percentages of patients who were outside the normal range at baseline and returned to within normal range after administration of MultiHance ranged from 22% to 57%.

### TABLE 4. AEs Reported in Subjects With Renal Impairment

<table>
<thead>
<tr>
<th>Impairment*</th>
<th>No (%) Patients</th>
<th>No (%) Patients</th>
<th>No (%) Patients</th>
<th>No (%) Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AE</td>
<td>533 (23)</td>
<td>385 (18)</td>
<td>215 (17)</td>
<td>161 (13)</td>
</tr>
<tr>
<td>No. subjects with AE</td>
<td>296 (23)</td>
<td>224 (18)</td>
<td>122 (18)</td>
<td>98 (14)</td>
</tr>
<tr>
<td>Intensity†</td>
<td>45 (20)</td>
<td>28 (16)</td>
<td>26 (20)</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Mild</td>
<td>225 (18)</td>
<td>182 (14)</td>
<td>81 (12)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>Moderate</td>
<td>48 (4)</td>
<td>25 (2)</td>
<td>17 (3)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>4 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>18 (1)</td>
<td>15 (1)</td>
<td>20 (3)</td>
<td>19 (3)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>9 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

*Categories of renal impairment are defined on the basis of urinary creatinine clearance (CrCL): no impairment (CrCL ≥ 80 mL/min); mild (50 mL/min ≤ CrCL < 80 mL/min), moderate (30 mL/min ≤ CrCL < 50 mL/min), and severe impairment (CrCL < 30 mL/min).

†Includes AE with definite, probable, possible, doubtful, remote, unknown or missing relationship to the study agent.

‡If more than one AE occurred, the maximum intensity was counted.
for total protein and albumin, and from 2% to 25% for other hepatic function parameters, indicating the possibility of laboratory and biologic variability in a setting of pathophysiologically diverse pre-existing conditions. Results of the retrospective safety analyses on liver enzymes in cirrhotic and noncirrhotic patients are presented in Table 5.

Liver function tests in the pediatric population (n = 110) indicated no cause for concern relating to deterioration of hepatic function after the administration of MultiHance. No clinically meaningful changes were observed from pre-dose to postdose, with the majority of the values within normal range at all time points. No postdose changes were considered markedly abnormal, and no postdose changes in liver function tests were assessed by the investigator as an adverse event.

**Cardiac Safety Assessment**

A total of 186 subjects were studied in cardiac imaging trials with MultiHance, most at a dose of 0.05 mmol/kg. In this subset of patients with CAD, the rate of AEs was greater than that in the overall adult population (67/186, 36% vs. 531/2982, 18%). Interestingly, the rate of the most commonly recorded AE was similar in the CAD population (headache 2% vs. 2% overall, nausea 1% vs. 2% overall), and the rate of some vascular and cardiac AE was similar or lower in this population (vasodilatation 0% vs. 1% overall, tachycardia 0.5% vs. 0.5% overall). In one placebo-controlled safety study in CAD patients, the rate of AE after MultiHance was comparable to the rate after injection of saline (Table 3).

Evaluation of intermittent 12-lead ECG data in 1045 patients enrolled in clinical trials with MultiHance revealed that most changes were in the <20 milliseconds range and distributed evenly between increases and decreases. In controlled trials, changes in ECG data were similar to those seen after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or placebo. Increases of potential clinical importance (after Omniscan or place
intervals above the normal range at baseline returned to within the normal range after administration of MultiHance; however, there was no explanation for this phenomenon.

No significant effect on ventricular repolarization could be observed. Most changes for QTc intervals were less than 20 milliseconds and evenly distributed between increases and decreases of the same magnitude indicating a degree of normal biologic variability. The changes were similar to those seen for placebo and Omniscan. These findings were consistent with those of a single-blind, placebo-controlled, randomized, crossover study designed to acquire and evaluate continuous ECG data in 47 subjects (healthy volunteers and patients with cardiovascular disease) that showed changes with 0.2 mmol/kg MultiHance were similar to those seen for matched volumes of placebo. 

Six subjects experienced nonserious incidental findings pertaining to conduction abnormalities during the intermittent ECG monitoring, 5 after MultiHance (1/2637, 0.2%) and 1 after saline (1/127, 0.8%). There was no evidence that MultiHance played a role in the creation of these mild AE. In the previously discussed pharmacokinetic study in children, mean values for ECG parameters (PR, QRS, QT, and QTc intervals) remained fairly constant over the 24-hour monitoring time period, and no changes of potential clinical importance were recorded.

**Postmarketing Safety Surveillance**

Spontaneously reported AE in 1,505,813 exposures with MultiHance were collected during the period from August 1, 1998, to July 31, 2005. During this time period, 761 patients reported a total of 1539 AE, for an estimated AE reporting rate of 0.05%. The majority of reactions reported were nonserious and consistent with those observed in the clinical trial experience. Reported AE were most likely to affect the gastrointestinal, dermal, or respiratory systems (Table 6). The 3 most frequently reported AE were urticaria, nausea, and vomiting, each with an estimated reporting rate of 0.02% or less. With the exception of a single reported case of hyperbilirubinemia, no spontaneous reports of liver toxicity related to MultiHance administration have been reported, which is significant given the partial hepatobiliary uptake of this agent. To date, 147 patients have experienced serious AE (0.01%), a reporting rate consistent with that observed for other gadolinium chelates such as Magnevist. Serious AE reported in conjunction with the administration of MultiHance are most likely to be associated with the respiratory system or the skin and subcutaneous tissues: the most frequently reported serious AE include dyspnea, nausea, urticaria, hypotension, and anaphylactoid reactions, each with an occurrence rate of 0.003% or less. No episodes of prolonged QT/QTc, malignant arrhythmias, or torsade de pointes have been reported, nor any AE that might be associated with QT/QTc prolongation and torsade de pointes.

**TABLE 6. Most Common AE Spontaneously Reported in Association with the Use of MultiHance**

<table>
<thead>
<tr>
<th>AE</th>
<th>No. Reports*</th>
<th>Reporting Rate†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>258</td>
<td>0.0171</td>
</tr>
<tr>
<td>Vomiting</td>
<td>115</td>
<td>0.0076</td>
</tr>
<tr>
<td>Urticaria</td>
<td>103</td>
<td>0.0068</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>56</td>
<td>0.0037</td>
</tr>
<tr>
<td>Erythema</td>
<td>55</td>
<td>0.0037</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>44</td>
<td>0.0029</td>
</tr>
<tr>
<td>Pruritus</td>
<td>44</td>
<td>0.0029</td>
</tr>
<tr>
<td>Hypotension</td>
<td>32</td>
<td>0.0021</td>
</tr>
<tr>
<td>Cough</td>
<td>30</td>
<td>0.0020</td>
</tr>
<tr>
<td>Dizziness</td>
<td>28</td>
<td>0.0019</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>25</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

*AE reported from August 1, 1998 through July 31, 2005.
†Reporting Rate = number of reports/exposures (1,505,813).

**DISCUSSION**

MultiHance has been available for clinical use in Europe since 1998 and was approved by the FDA in late 2004. Like Magnevist (Gd-DTPA), MultiHance consists of a linear chelate of DTPA complexed with gadolinium. However, unlike Magnevist and the other gadolinium-based agents on the market, gadobenate dimeglumine (the active ingredient of MultiHance), possesses a hydrophobic benzoxymethyl substituent that results in partial hepatobiliary uptake and a 2-fold T1 relaxivity compared with other available gadolinium contrast agents. These unique properties have been shown to result in improved MRI of the central nervous system, vasculature system, breast, and liver compared with that observed with the use of other approved MR contrast agents. Previously, Kirchin et al demonstrated that the overall rate of AE in clinical trials with MultiHance was comparable to that reported for other agents such as Magnevist.

The most direct approach to comparing the safety of different gadolinium contrast agents is through the use of controlled trials in which an agent is compared directly against another agent in the same study (ie, by means of parallel-group or within-patient crossover study designs, in which each patient acts as his/her control). A series of such studies comparing MultiHance with Magnevist has shown that the safety profile of these 2 agents is very similar (AE rate 8% for MultiHance and 9% for Magnevist, P = 0.84). These results agree with previous studies in which a similar overall incidence of AE has been noted in studies comparing Magnevist with ProHance, Omniscan, Dotarem, or OptiMARK. None of these studies showed a discernible difference between the various gadolinium-based MRI contrast agents in terms of the incidence or type of AE reported. Excellent safety also was demonstrated in a comparison trial with Magnevist in children with CNS disease, with the overall incidence of AE similar between MultiHance (12.9%) and Magnevist (14.6%). On the basis these data, MultiHance appears to be safe for use in adults and children at a dose of 0.1 mmol/kg.

No significant risk is expected when MultiHance is administered in patients with renal or hepatic impairment. The rate and type of AE recorded after MultiHance in subjects with renal impairment (5/20, 25%) were comparable to those recorded in subjects given a saline placebo (5/12, 5%), which is similar to the rate reported for other gadolinium-based agents.
42%) and to normal subjects studied in a previous pharmacokinetic study with MultiHance.\textsuperscript{17,22} Despite the partial hepatobiliary uptake and excretion of MultiHance, an exhaustive assessment of laboratory and adverse event data revealed no pattern of liver toxicity or worsening liver function after the administration of MultiHance in either the adult or pediatric population. This was true both for the clinical trial population as a whole and in subgroups of patients stratified by the degree of severity of pre-existing liver disease.

No detrimental effect on cardiac electrophysiology could be observed from a retrospective analysis of ECG parameters in more than 1000 patients and healthy volunteers, as well as from a placebo-controlled study with continuous 24-hour ECG monitoring of patients with cardiovascular disease who had received a high dose (0.2 mmol/kg) of MultiHance.\textsuperscript{25}

Several gadolinium chelates are known to cause falsely lowered readings of serum calcium levels when automated complexometric techniques are used. This phenomenon has been called “spurious hypocalcemia” by Prince et al,\textsuperscript{39} who observed decreases from normal serum calcium levels in as many as 16% of patients given Omniscan. Spurious laboratory values (either increases or decreases) have been reported for other gadolinium agents such as OptiMARK. Distortion of laboratory assays are thought to be due to dissociation of the gadolinium chelate complex in vivo or the binding of calcium by excess chelate contained in the formulations of some marketed gadolinium contrast agents.\textsuperscript{39,40} A recent study evaluated the effect of MultiHance and Magnevist on the measurement of calcium in serum or plasma.\textsuperscript{41} At clinically relevant concentrations neither of these agents produced interferences with the colorimetric determination of calcium, whereas Omniscan and OptiMARK produced strong interferences.

**CONCLUSIONS**

The safety of MultiHance has been assessed in more than 3000 subjects enrolled in clinical trials and in more than 1.5 million patients in postmarketing surveillance. Despite some properties that distinguish MultiHance from other gadolinium-based contrast agents, the safety of this agent is comparable to that of the other FDA-approved gadolinium agents. MultiHance appears to be quite safe for use in children, and in patients with renal impairment, hepatic impairment, or cardiac disease.

**REFERENCES**


