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Macrocyclic MR contrast agents: evaluation of multiple-organ gadolinium retention in healthy rats

Simona Bussi[1*], Alessandra Coppo[1], Roberto Celeste[1], Antonello Fanizzi[1], Alberto Fringuello Mingo[1], Andrea Ferraris[2], Catherine Botteron[3], Miles A. Kirchin[4], Fabio Tedoldi[1] and Federico Maisano[2]

Abstract

Objectives: The purpose of this study was to compare Gd levels in rat tissues after cumulative exposure to four commercially available macrocyclic gadolinium-based contrast agents (GBCAs).

Methods: Sixty-five male Sprague-Dawley rats were randomized to four exposure groups ($n = 15$ per group) and one control group ($n = 5$). Animals in each exposure group received 20 GBCA administrations (four per week of ProHance®, Dotarem®, Clariscan™, or Gadovist® for 5 consecutive weeks) at a dose of 0.6 mmol/kg bodyweight. After 28-days' recovery, animals were sacrificed and tissues harvested for Gd determination by inductively coupled plasma-mass spectroscopy (ICP-MS). Histologic assessment of the kidney tissue was performed for all animals.

Results: Significantly ($p \leq 0.005$; all evaluations) lower Gd levels were noted with ProHance® than with Dotarem®, Clariscan™, or Gadovist® in all soft tissue organs: 0.144 ± 0.015 nmol/g vs. 0.342 ± 0.045, 0.377 ± 0.042, and 0.292 ± 0.047 nmol/g, respectively, for cerebrum; 0.151 ± 0.039 nmol/g vs. 0.315 ± 0.04, 0.345 ± 0.053, and 0.316 ± 0.040 nmol/g, respectively, for cerebellum; 0.361 ± 0.106 nmol/g vs. 0.685 ± 0.330, 0.823 ± 0.495, and 1.224 ± 0.664 nmol/g, respectively, for liver; 38.6 ± 25.0 nmol/g vs. 172 ± 134, 212 ± 121, and 294 ± 127 nmol/g, respectively, for kidney; and 0.400 ± 0.112 nmol/g vs. 0.660 ± 0.202, 0.688 ± 0.215, and 0.999 ± 0.442 nmol/g, respectively, for skin. No GBCA-induced macroscopic or microscopic findings were noted in the kidneys.

Conclusions: Less Gd is retained in the brain and body tissues of rats 28 days after the last exposure to ProHance® compared to other macrocyclic GBCAs, likely due to unique physico-chemical features that facilitate more rapid and efficient clearance.

Keywords: Contrast media, Magnetic resonance imaging, Gadolinium, Pharmacokinetics, Histology, Rats

Key points

- Macrocyclic gadolinium-based contrast agents (GBCAs) differ in their propensity for Gd retention in rat tissues and organs
- The level of retained Gd may reflect the ease and rapidity of Gd clearance from tissues and organs after administration
- Macrocyclic GBCAs have no impact on rat kidney tissue histology, up to the tested cumulative dose of 12 mmol/kg

Introduction

It is well established that trace amounts of gadolinium (Gd) are retained in brain and body tissues following the administration of both linear and macrocyclic gadolinium-based contrast agents (GBCAs) [1, 2]. Although the nature of the retained Gd has still to be elucidated, there is strong evidence that GBCAs enter into brain tissues predominantly in the cerebrospinal fluid (CSF) and that Gd retention occurs following its passage from the perivascular space to the interstitial space as

* Correspondence: simona.bussi@bracco.com
[1]Bracco Imaging SpA, Bracco Research Centre, Via Ribes 5, 10010 Colleretto Giacosa, TO, Italy
Full list of author information is available at the end of the article

part of the normal glymphatic system [3–7]. This mechanism may explain why Gd is retained in the human brain even in the absence of intracranial abnormalities potentially affecting blood-brain barrier permeability [8].

Whereas early reports focused primarily on differences between linear and macrocyclic GBCAs [9, 10], it is now apparent that there are differences also amongst GBCAs of the same class [11–13]. In a recent comparison of three macrocyclic GBCAs in rodents, Bussi et al. [12] ascribed lower levels of Gd retention in the brain after gadoteridol (ProHance®; Bracco Imaging) to differences in the physico-chemical properties of the GBCAs, postulating that the low molecular weight of gadoteridol, combined with lower viscosity and slightly higher lipophilicity [14] compared to gadobutrol (Gadovist®; Bayer Healthcare) [15] and gadoterate (Dotarem®; Guerbet) [16] may facilitate its more efficient clearance via the glymphatic system.

Recently, a fourth macrocyclic GBCA (Clariscan™, gadoteric acid; GE Healthcare) has become available in some countries. This GBCA has the same formulation as Dotarem® [17] but has never been included in either clinical or non-clinical studies of Gd retention. The aim of our study was to confirm and extend the findings of Bussi et al. [12] by assessing the extent to which Gd is retained in rat brain and body tissues after serial administration not only of Dotarem®, Gadovist®, and ProHance® but also of the newer GBCA Clariscan™. At variance with the study of Bussi et al. [12], we adopted validated analytical methods with lower limits of quantification for liver and skin samples to determine whether significant differences in Gd retention are also seen in these tissues. Additional novel aims were to evaluate microscopically the possible impact of these GBCAs on kidney tissue histology and to assess whether there is any influence of GBCA osmolarity (specifically Gadovist 0.5 M vs. Gadovist 1.0 M) on the levels of Gd retention. Finally, we performed computational studies to determine whether hydration-related parameters of the three macrocyclic molecules correlate with Gd clearance from tissues.

Materials and methods

We followed the methods of Bussi et al. [12]. The study was performed at Charles River Lyon, France (AAALAC accredited), according to site-specific procedures established by the relevant Quality Assurance Unit. Procedures were conducted according to national and international regulations (L.D. 26/2014; Directive 2010/63/EU), Decree 2013-118 relating to the protection of animals used in scientific experiments described in the Journal Officiel de la République Française on 01 February 2013.

Animal study

Sixty-five male Sprague-Dawley OFA (SD) rats (Charles River Laboratories, France) aged 6 weeks and weighing 129.0–232.5 g at the start of treatment were utilized. After 8 days of acclimation, the animals were randomized to one of five groups: group A (saline; $n = 5$), group B (ProHance®; $n = 15$), group C (Dotarem®; $n = 15$), group D (Clariscan™; $n = 15$), and group E (Gadovist®; $n = 15$). Gadovist® was diluted 1:1 with water for injection (WFI) prior to injection to achieve a similar concentration (0.5 M) and administered volume to those of the other GBCAs investigated. Animals were housed under controlled conditions at 22 ± 3 °C, > 35% relative humidity and 12 h dark/light cycles. Food pellets (A04C-10; Safe, France) and filtered water from municipal services were provided ad libitum.

Animals in groups B, C, D, and E were administered the following contrast agents, respectively: ProHance®, batch n. V17628, expiry: 06/2020; Dotarem®, batch n. 17GD009B01, expiry: 01/2020; Clariscan™, batch n. 13794731, expiry: 12/2018; Gadovist® batches n. 44617D and 72649A, expiry: 11/2017 and 05/2020, respectively. Administration of GBCA or saline was performed at room temperature at the same time each day (between 8.00 a.m. and 12.00 a.m.) into the lateral vein of the tail at an injection rate of 2 mL/min using a Harvard infusion pump. All animals received saline solution (0.9% w/v NaCl) or the respective GBCA at 1.2 mL/kg bodyweight four times a week for 5 consecutive weeks, for a total cumulative dose of 12 mmol/kg bodyweight. The daily administered dose (0.6 mmol/kg bodyweight) corresponds to a clinical dose of 0.1 mmol/kg bodyweight, based on the extrapolation factor for rats [18]. After the 5-week treatment period, each animal was allowed a recovery period of 28 days (corresponding to approximately 2.5 human years [19, 20]) before sacrifice.

Observations

During the treatment period, all animals were inspected before and after dosing for any clinical signs or reactions to treatment. During the treatment-free period, all animals were inspected once daily. A full clinical examination was performed pre-test and then weekly during the treatment and treatment-free periods.

Pathology

At the end of the treatment-free period, all animals were necropsied. The animals were killed by carbon dioxide inhalation and exsanguination. After exsanguination and blood sampling, a complete macroscopic post-mortem examination was performed; abnormal findings, if any, were recorded. Thereafter, each animal was dissected to obtain tissues (cerebrum, cerebellum, liver, right kidney, right femur, and skin) for inductively coupled plasma-mass spectrometry (ICP-MS) determination of gadolinium. A total of 455 tissue/blood samples were collected (65 animals; 6 tissue samples, and 1 blood sample per

animal). At the same time, the left kidney was dissected and processed to slides for histopathologic evaluation by an experienced ECVP-qualified pathologist (Charles River Laboratories, France).

Determination of total gadolinium

All procedures were carried out at Bracco Research Centre (Colleretto Giacosa, Turin, Italy). Blood samples (0.5 mL) were mixed 1:2 with nitric acid (65% w/w, Extrapure, Merck). Cerebrum and cerebellum samples were weighed and freeze-dried, and then suspended in 1 mL of nitric acid. The liver, kidney, and skin samples were weighed, freeze-dried, and ground in a mortar. Approximately 0.2 g of each organ was then weighed and suspended in 1 mL of nitric acid. Femurs were weighed and dissolved in 1 mL of nitric acid. All nitric acid solutions were stored at 4 °C for at least 12 h before digestion. Sample mineralization was performed by subjecting the samples to a wet ashing process (95 min at 180 °C for blood, 110 min at 180 °C for the other organs) in a microwave oven system (MARS-5; CEM Corporation). The mineralized samples were quantitatively transferred to disposable Falcon tubes, diluted to 20 mL with 2% nitric acid, filtered at 0.45 μm, and then analyzed by ICP-MS using validated analytical methods. Internal standardization was performed using ^{153}Eu. The calibration blanks, calibration standards, and control standard solutions for each analytical sequence were prepared in 2% nitric acid by dilution of a gadolinium oxide (Gd_2O_3) standard solution (1000 μg/mL in 2% HNO_3, Certipur, Merck).

The lower limit of quantitation (LOQ) for gadolinium was 0.1 nmol/mL for blood, 0.1 nmol/g for cerebrum/cerebellum, 0.6 nmol/g for femur, and 1.5 nmol/g for kidney. The LOQ for each of these tissues was verified for accuracy and precision by spiking in triplicate explanted blank organs from untreated animals (not included in this study) with the corresponding amounts of gadolinium and determining the respective percent recoveries. For liver and skin, the LOQ was determined to be 0.1 nmol/g. For these two tissues, the reported values were extrapolated concentrations for samples in which the signal-to-noise (S/N) ratio was at least 10, with the noise corresponding to the mean tissue signal in saline-treated control animals. These extrapolated values were considered conservative, since both the European Medicines Agency (EMA) [21] and Food and Drug Administration (FDA) [22] recommend that the analyte response at the LOQ is at least five times the zero calibrator.

Assessment of kidney tissue histology

The left kidney of all animals was dissected and fixed in 10% neutral formalin for slide preparation. All slides were stained with hematoxylin and eosin. If abnormal findings were observed, these were graded using a five-point scale from 1 (minimal/very few/very small) to 5 (massive/very many/very large).

Computational studies

Computational studies were performed to determine whether the minor structural differences between the macrocyclic GBCA molecules impact hydration-related parameters (hydrophilic surface and solvation enthalpy), which reflect the tendency to form ionic or hydrogen bonds primarily with water, but possibly also with hydrophilic macromolecules of the extracellular matrix in body tissues. The hydrophilic surface is a partition of the space around the molecule that defines regions open to interaction with water molecules; the higher the hydrophilic surface value, the higher the number of interactions. The interactions with water molecules can be of different nature (ion-dipole, hydrogen bonding, van der Waals forces), meaning that different energy (enthalpy) levels are released when the molecule is put in water (hydrated). Calculation of hydrophilic surface and solvation enthalpy for gadoterate, gadobutrol and gadoteridol was based, as starting geometries, on the crystallographic structures of the molecules [23–25]. All ab initio calculations were performed at the restricted Hartree-Fock level with the Gaussian 09 W program [26] using the (1 s-4d, 4f7) effective core pseudopotentials with the 5s4p3d-Gaussian-type orbitals valence basis set for the Gd atom [27]. Full geometry optimization of the starting structures was carried out with the 3-21G basis set for the atoms of the ligands, considering one inner-sphere water molecule ($q = 1$).

On the optimized structures, solvation energy was determined by means of single point energy calculations performed with the 6-31G** basis set for the other atoms of the ligands, both in vacuo and in solution, by adopting the polarizable continuum model as implicit solvation model [28]. Hydrophilic surface area values were calculated at the Molecular Mechanics level on the ab initio optimized structures, by means of Goodford's GRID algorithm [29], as implemented in the Maestro software package [30].

Statistical analysis

Gadolinium concentration was expressed as nanomoles per gram wet tissue in the case of cerebrum, cerebellum, liver, femur, kidneys, and skin and as nanomoles per milliliter in the case of blood. The Dixon test [31, 32] was used before formal data analysis to highlight possible anomalous data points. Levene's test [33] was used to test the equality of variance across groups and Shapiro-Wilk's test [34] was used to assess the normality of the data distribution in each group. Data with

homogeneous variances and normal distribution in all groups were analyzed using ANOVA followed by Dunnett's test [35]. Data showing non-homogeneous variances or a non-normal distribution in at least one group were analyzed using the Kruskal-Wallis test followed by Wilcoxon's rank-sum test [35]. All statistical analyses were performed at Charles River Laboratories, using SAS software, version 8.2 (Cary, USA).

Results

All animals successfully underwent all aspects of the study. No unexpected changes in bodyweight were noted and no adverse signs or symptoms were observed for any animal. No gross pathological tissue changes were noted at sacrifice.

The mean (± SD) Gd contents across groups and tissue types are presented in Fig. 1 and Table 1. After the 28-day recovery period, the mean Gd levels in the blood of all groups and in all organs from the control group were below the LOQ. Conversely, measurable amounts of Gd were detected in all the tested organs, but with marked differences across the GBCA groups.

The highest mean Gd levels in the cerebrum and cerebellum were noted after Clariscan followed by Dotarem and Gadovist and finally ProHance. The Gd levels after ProHance were significantly ($p \leq 0.005$; all evaluations) lower than the levels noted with Dotarem, Clariscan, and Gadovist in both the cerebrum (0.144 ± 0.0147 nmol/g vs. 0.342 ± 0.0448 nmol/g, 0.377 ± 0.0421 nmol/g, and 0.292 ± 0.0473 nmol/g, respectively) and cerebellum (0.151 ± 0.0393 nmol/g vs. 0.315 ± 0.0400 nmol/g, 0.345 ± 0.0525 nmol/g, and 0.316 ± 0.0397 nmol/g, respectively). The Gd level after Gadovist in the cerebrum was higher than after ProHance but significantly lower than after Dotarem ($p \leq 0.01$) and Clariscan ($p \leq 0.005$). The difference between Dotarem and Clariscan was not significant ($p > 0.05$) in the cerebellum but was just beyond the limit of significance in the cerebrum (0.342 ± 0.045 nmol/g and 0.377 ± 0.042 nmol/g, respectively; $p = 0.044$).

Similar findings were noted in the right kidney and liver. Significantly lower ($p \leq 0.005$; all evaluations) Gd levels were noted after ProHance than after Dotarem, Clariscan, and Gadovist in both tissues (38.6 ± 25.0 nmol/g vs. 172 ± 134 nmol/g, 212 ± 121 nmol/g, and 294 ± 127 nmol/g in the right kidney, respectively, and 0.361 ± 0.106 nmol/g vs. 0.685 ± 0.330 nmol/g, 0.823 ± 0.495 nmol/g, and 1.22 ± 0.664 nmol/g in the liver, respectively). Unlike in the cerebrum, the mean Gd level for Gadovist was significantly higher ($p \leq 0.05$) than that for Dotarem in the right kidney and both Dotarem ($p \leq 0.01$) and Clariscan ($p \leq 0.05$) in the liver.

Analogous results were found in the skin. The Gd level after ProHance (0.400 ± 0.112 nmol/g) was significantly lower ($p \leq 0.005$; all evaluations) than after Dotarem (0.660 ± 0.202 nmol/g), Clariscan (0.688 ± 0.215 nmol/g), and Gadovist (0.999 ± 0.442 nmol/g). The value for Gadovist was significantly higher than that for both Dotarem ($p \leq 0.01$) and Clariscan ($p \leq 0.05$).

In the femur, significantly higher ($p \leq 0.005$, all evaluations) Gd levels were noted with Gadovist than with ProHance, Dotarem, and Clariscan (16.1 ± 4.51 nmol/g vs. 8.48 ± 1.87 nmol/g, 6.28 ± 3.08 nmol/g, and 9.44 ± 4.01 nmol/g, respectively). No significant differences were noted between ProHance, Dotarem, and Clariscan.

Assessment of kidney tissue histology

There were no microscopic observations and no abnormal findings in the left kidney that were considered to be associated with any of the GBCAs (Fig. 2). Any observations were considered incidental and within the range of expected spontaneous changes in rats.

Computational studies

We calculated the hydrophilic surface and hydration enthalpy for the gadoterate, gadobutrol, and gadoteridol molecules, as indicators of the number and strength of hydrogen bonds and ionic interactions established during dissolution (Table 2). The lowest absolute values in both cases were obtained for gadoteridol.

Discussion

No clinical signs, symptoms, or adverse clinical outcomes have yet been associated with retained Gd in the brain following the repeated administration of any GBCA [36, 37]. Nevertheless, because macrocyclic GBCAs as a class have been associated with lower levels of Gd retention in animal studies [9–11, 13], and with only minor/negligible increases in T1-signal in the dentate nucleus or globus pallidus on unenhanced T1-weighted brain images [38–40] when compared with certain linear GBCAs, the perception is that macrocyclic GBCAs are in some way "safer." Consequences of this perception have been the suspension by the EMA in Europe of all general-purpose linear agents, and the widespread assumption that all GBCAs within each class are essentially similar and interchangeable. That this is not the case has been highlighted by several recent studies that have shown significant differences amongst GBCAs of the same class in terms of the levels of Gd retained [11–13].

Tissue Gd concentrations

Our results confirm and extend those of Bussi et al. [12] in showing significantly lower (between 2 and 2.6 times lower) levels of Gd in rat brain (cerebrum and cerebellum) after cumulative administration of ProHance than after equivalent cumulative administration of Dotarem, Clariscan, or Gadovist. These findings have additionally

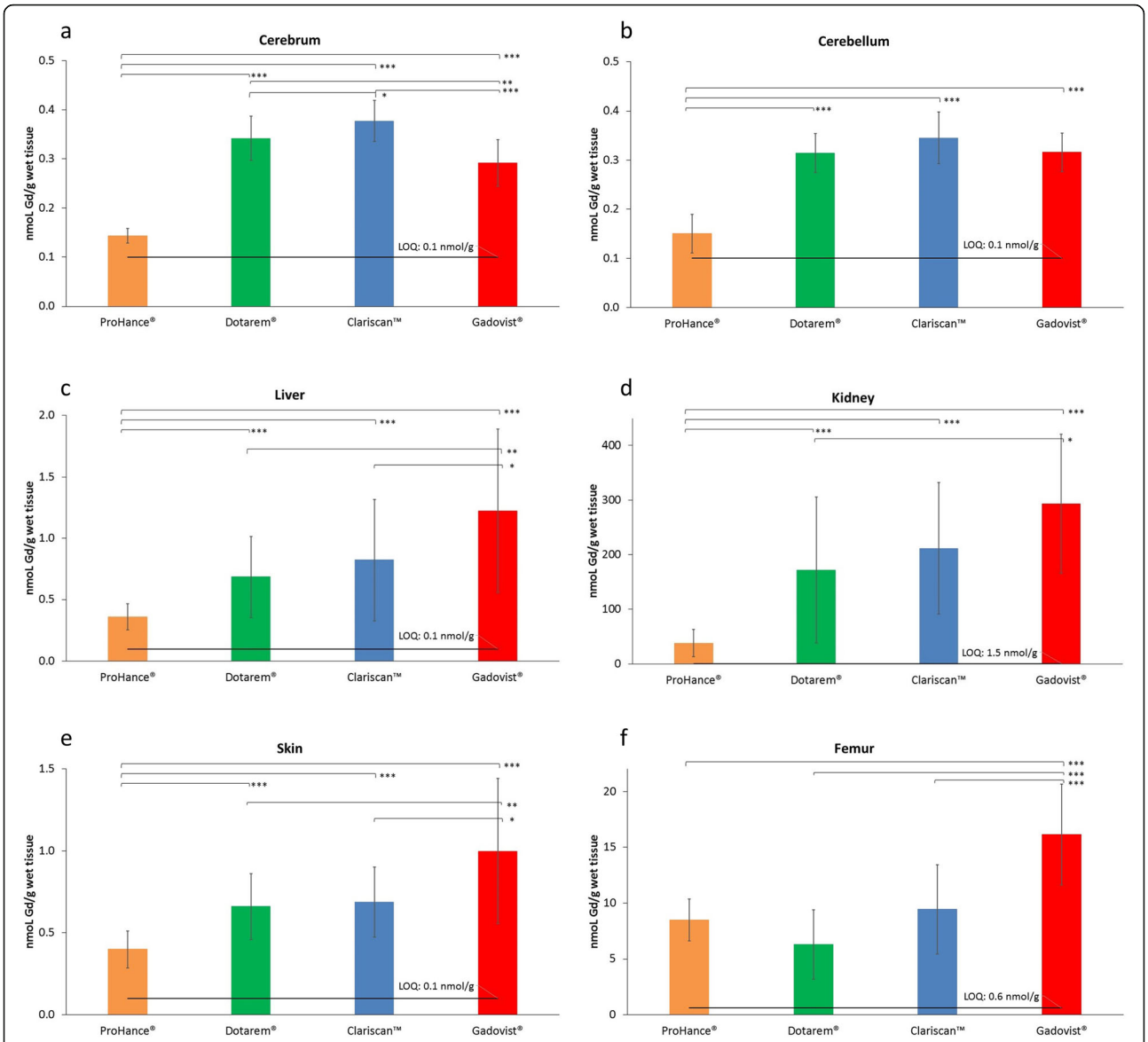

Fig. 1 Gadolinium content in the (**a**) cerebrum, (**b**) cerebellum, (**c**) liver, (**d**) kidney, (**e**) skin, and (**f**) femur. Mean values ± SD. The significance of differences between groups is shown as $*p \leq 0.05$, $**p \leq 0.01$, and $***p \leq 0.005$. Data for blood and for the control group (group A, saline) are not shown because all values were below the LOQ. The error bars represent the standard deviation of measurements within the groups ($n = 15$, except "Dotarem, skin" and "Gadovist, kidney" where $n = 14$)

been confirmed by Jost et al. [13] who reported roughly threefold lower levels of Gd in rat cerebellum after ProHance than after Dotarem or Gadovist (0.19 nmol/g vs. 0.54 nmol/g and 0.63 nmol/g, respectively) at 5 weeks, after 8 administrations of each GBCA at 1.8 mmol/kg per injection. Although the retained Gd levels were similar for the three macrocyclic GBCAs at 26 and 52 weeks after the last administration [13], these findings suggest that ProHance is cleared more rapidly than Dotarem or Gadovist, possibly reflecting more efficient migration of the gadoteridol molecule towards the venous and lymphatic vessels in the interstitial space. In this regard, it appears molecular migration is promoted not only by convection, which is unaffected by small differences in otherwise similar molecules, but also by diffusion, which is highly dependent on the intrinsic molecular properties of the GBCAs and their capacity for interaction with the complex surrounding matrix [41].

Gd clearance from soft tissues

As noted in Bussi et al. [12], of the three macrocyclic molecules investigated, gadoteridol has a low molecular

Table 1 Gadolinium content in the blood, cerebrum, cerebellum, liver, kidney, skin, and femur (mean values ± SD)

Group (ID)	Blood (nmol/mL)	Cerebrum (nmol/g)	Cerebellum (nmol/g)	Liver (nmol/g)	Kidney (right) (nmol/g)	Skin (nmol/g)	Femur (nmol/g)
Control (A)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
ProHance (B)	< LOQ[a]	0.144 ± 0.015[b]	0.151 ± 0.039	0.361 ± 0.106	38.6 ± 25.0	0.400 ± 0.112	8.48 ± 1.87
Dotarem (C)	< LOQ	0.342 ± 0.045$^{°°°}$	0.315 ± 0.040$^{°°°}$	0.685 ± 0.330$^{°°°}$	172 ± 134$^{°°°}$	0.660 ± 0.202$^{°°°}$	6.28 ± 3.08
Clariscan (D)	< LOQ	0.377 ± 0.042$^{°°,*}$	0.345 ± 0.053$^{°°°}$	0.823 ± 0.495$^{°°°}$	212 ± 121$^{°°°}$	0.688 ± 0.215$^{°°°}$	9.44 ± 4.01
Gadovist (E)	< LOQ	0.292 ± 0.047$^{°°°,**,###}$	0.316 ± 0.040$^{°°°}$	1.22 ± 0.664$^{°°°,**,#}$	294 ± 127$^{°°°,*}$	0.999 ± 0.442$^{°°°,**,#}$	16.1 ± 4.51$^{°°°,***,###}$

$n = 5$ for control animals; $n = 15$ for all other groups except "Dotarem, skin" and "Gadovist, right kidney" where $n = 14$
Significance vs. group B (ProHance): $^{°°}p \le 0.01$, $^{°°°}p \le 0.005$; vs. group C (Dotarem): $^{*}p \le 0.05$, $^{**}p \le 0.01$, $^{***}p \le 0.005$; vs. group D (Clariscan): $^{\#}p \le 0.05$, $^{\#\#\#}p \le 0.005$
[a]1 out of 15 values > LOQ (0.165)
[b]7 out of 15 values < LOQ

weight and other properties that would favor fewer interactions with the surrounding matrix and thus more rapid diffusion and clearance than is the case with gadobutrol and gadoterate. Specifically, since all three molecules are hydrophilic, any interactions with the surrounding matrix that would hinder diffusion leading to slower clearance are likely to occur through hydrogen bonding (e.g., with collagen) and ionic interactions (e.g., with proteoglycan-associated cations). With regards to hydrogen bonding, the gadoteridol molecule carries only one hydroxy group, while the gadobutrol molecule carries three (Fig. 3). As a result, fewer hydrogen bonds are to be expected with gadoteridol than with gadobutrol, resulting in fewer interactions with the surrounding matrix. Likewise, the gadoteridol molecule is non-ionic and thus would be expected to have fewer electrostatic interactions with components of the extracellular matrix than the ionic gadoterate molecule which carries a net negative charge [42]. Our findings for the hydrophilic surface and hydration enthalpy of the three molecules lend support to the initial findings of Bussi et al. [12]. Both these parameters are indicators of the number and strength of hydrogen bonds and ionic interactions established during dissolution in water. The lowest absolute values in both cases were obtained for gadoteridol (Table 2), suggesting that the propensity to establish dipole-dipole interactions with macromolecules rich in hydrogen donor/acceptor groups or ionic charges is lower for gadoteridol than for gadobutrol and gadoterate, respectively.

Of notable interest, we also found significantly lower Gd levels in kidney, liver, and skin after ProHance than after all other GBCAs. Given the strikingly similar profiles of the measured GBCA levels across all soft tissue organs, with ProHance consistently returning lower levels of retained Gd, it is likely the unique physico-chemical properties of the gadoteridol molecule may be relevant not only in the brain [12, 13] but also across all soft tissues.

Gd levels in bone

Our findings for Gd levels in the femur confirm those of Bussi et al. [12] with significantly higher ($p \le 0.005$, all evaluations) levels for Gadovist and non-significantly lower levels for Dotarem relative to ProHance and Clariscan. As in other tissues, the higher Gd levels with Gadovist in bones may reflect increased hydrogen bonding of the gadobutrol molecule with collagen-rich regions [45]. Notably, Lord et al. [46] recently reported Gd levels in the bones of subjects exposed to Gadovist that

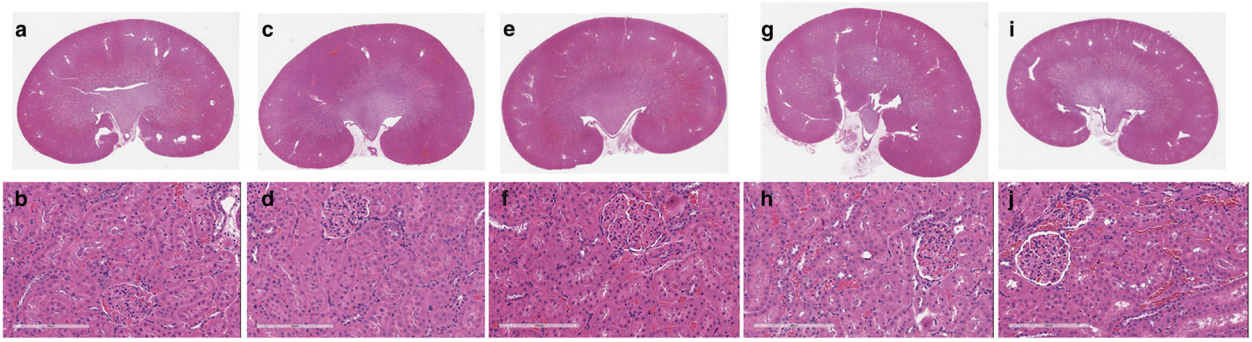

Fig. 2 Representative overviews and high magnifications (bar = 200 μm) of kidneys from control animals (**a** and **b**) and from animals administered a total cumulative dose of 12 mmol/kg bodyweight of ProHance (**c** and **d**), Dotarem (**e** and **f**), Clariscan (**g** and **h**), and Gadovist (**i** and **j**). None of the kidneys showed any histologic abnormalities

Table 2 Physico-chemical features of the gadoterate, gadobutrol, and gadoteridol molecules

	Gadoterate (Dotarem/Clariscan)	Gadobutrol (Gadovist)	Gadoteridol (ProHance)
k_d (s^{-1})[a]	7.17×10^{-14}	1.11×10^{-12}	1.15×10^{-11}
$t_{½}$ (years)[b]	306,549	19,801	1911
Hydrophilic Surface ($Å^2$)	491	404	353
Solvation enthalpy (kcal/mol)	-36	-12	-9

[a] k_d are the rate constants that characterize the dissociation of GBCA complexes in 0.15 M NaCl at 25 °C and pH = 7.4 [43, 44]
[b] $t_{½}$ is the half-life (years) of the dissociation reactions of GBCA complexes in 0.15 M NaCl at 25 °C and pH = 7.4 ($t_{½} = \ln 2/k_d$) [43, 44]

were not dissimilar to the level reported for a subject exposed to the linear GBCA Omniscan, which is known to lead to greater Gd retention in bones than ProHance [47–49]. The lack of any relevant differences for gadoterate and gadoteridol may be because the extracellular matrix is mineralized in bones, which prevents water flow or diffusion and excludes the contribution of these phenomena to product clearance.

Histologic evaluation of kidney tissue

Amongst the tissues evaluated, the highest levels of Gd were noted in the kidney, presumably reflecting the fact that this organ is directly involved in GBCA elimination. As in liver and skin, the lowest levels were noted for ProHance followed by Dotarem and Clariscan and finally Gadovist. These findings again confirm those of Bussi et al. [12] and are supported by results from McDonald et al. [11] who found markedly higher median Gd levels in rat kidney at 7 days after 20 administrations of 2.5 mmol/kg Gadovist (555 μg Gd/g of tissue) than after the same dose of ProHance (168 μg Gd/g of tissue).

At variance with our findings, McDonald et al. [11] found more advanced ultrastructural changes in kidneys of ProHance-exposed animals than in kidneys of animals exposed to Gadovist, MultiHance, and Omniscan. These changes included advanced loss of the normal cytoarchitecture of the proximal convoluted tubule, alterations in glomerular structure and filling of Bowman space with matrix and cellular debris, and loss of the outer mitochondrial membrane [11]. Our study revealed no evidence of any macroscopic or microscopic alterations of renal tissues with any GBCA relative to control animals and no evidence of any specific difference with ProHance relative to the other macrocyclic GBCAs. Rather than reflecting a cytotoxic effect of ProHance, the histologic findings described by McDonald et al. [11] are more suggestive of a rat-specific pathology called chronic progressive nephropathy (CPN) [50, 51], and it is possible that the relatively harsh treatment regimen utilized (a cumulative dose of 50 mmol/kg) led to exacerbation of CPN in certain rats. Importantly, CPN has no human counterpart and is not relevant for extrapolation in human risk assessment [52].

Effects of GBCA formulation properties

Our study differed from that of Bussi et al. [12] in that we included Clariscan for the first time in a Gd retention study and diluted the Gadovist formulation 1:1 with WFI prior to injection. Moreover, thanks to the lower LOQ of the ICP-MS analytical method, we report here also Gd levels in the skin and liver. A comparison of Gd levels across all tissues revealed consistently slightly higher mean levels after Clariscan than after Dotarem although borderline statistical significance ($p = 0.044$) was attained only in the cerebrum. Since the two GBCAs are formulated similarly, the reason for the slight difference

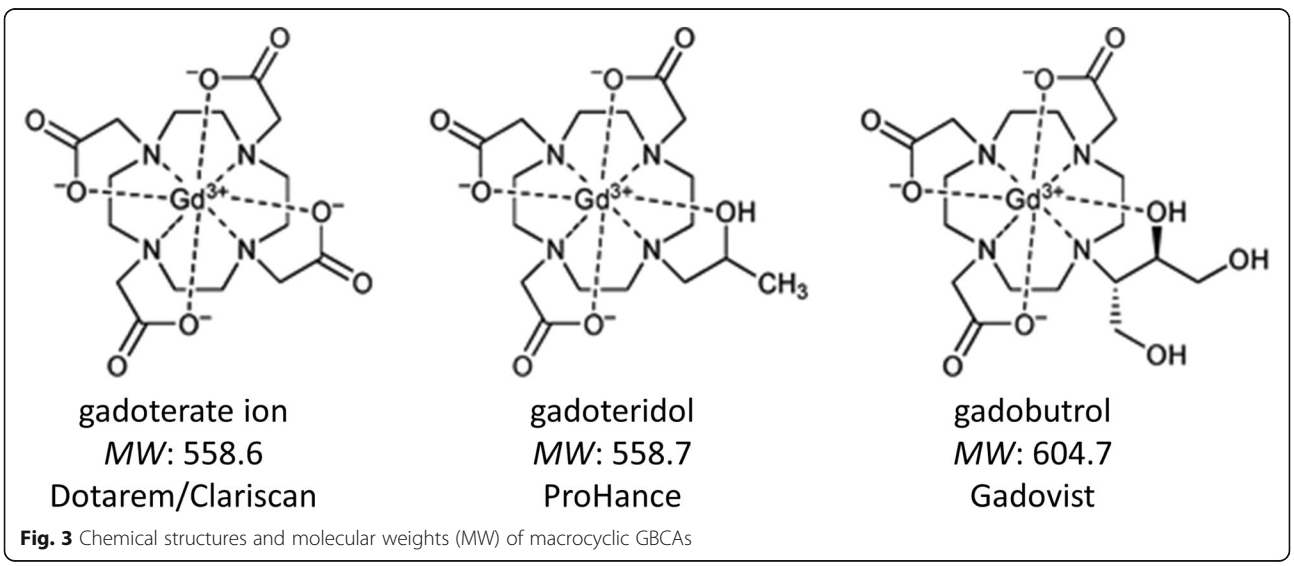

Fig. 3 Chemical structures and molecular weights (MW) of macrocyclic GBCAs

is unclear and should be the subject of further study. Concerning the dilution of Gadovist, this was performed to rule out the possibility that the higher Gd levels in brain tissue observed by Bussi et al. [12] were due to a transient osmotic shock of the blood-brain or blood-CSF barriers caused by the higher concentration of the Gadovist formulation. That the brain Gd levels in our study and in that of Bussi et al. [12] were both approximately twofold higher with Gadovist compared to ProHance suggests that transient osmotic shock is not a reason for the higher Gd levels observed with Gadovist.

Chelate stability

A final consideration concerns the stabilities of the different macrocyclic agents. In all cases, the dissociation half-life exceeds 1900 years at 25 °C in 0.15 M NaCl (Table 2). That none of the agents would dissociate at any point during a patients' lifetime is suggested by Birka et al. [53] who determined trace levels of intact gadoteridol in the skin of a patient on dialysis who had received ProHance 8 years earlier. That ProHance does not dissociate was also suggested by Gianolio et al. [54] who noted that the amount of residual intact gadoteridol in rat brain after repeat administrations of ProHance corresponded to the total amount of retained Gd. These findings imply that differences between macrocyclic agents in terms of thermodynamic and kinetic stability are irrelevant and have no impact on the levels of retained Gd.

Study limitations

As with all animal studies, our findings are merely suggestive of the human clinical situation rather than definitive. Healthy animals cannot entirely reproduce the complex physiologic situation in humans and such limitations and restrictions should be borne in mind when decisions are made regarding GBCA usage and safety. For example, whereas Jost et al. [3] reported near-complete clearance of all GBCAs from rat CSF at 24 h after a threefold human equivalent dose of 1.8 mmol/kg bodyweight, Nehra et al. [6] reported significant Gd levels in human CSF at 24 days after a single standard clinical dose of 0.1 mmol/kg intravenous Gadovist. On the other hand, comparative studies can point to inherent differences between GBCAs, which might translate to the human clinical situation even if the precise human physiologic situation differs. Our results confirm those of others [11–13, 47] in noting lower overall Gd levels in animal tissues after repeated exposure to ProHance than after similar repeated exposure to other GBCAs.

A further possible limitation of our study is that Gd levels were determined at only one time point, 28 days, after the last GBCA administration. A recent review [55] suggested that measurements be made at both early (days/weeks) and late (1–2 years) time points after the last administration, since Gd clearance from brain tissue is a relatively slow process. Apart from issues concerning the duration, cost, ethics, and practicality of such studies, a drawback of this approach is the vastly different timescales of the lifespans of rats and humans [19, 20]. Given that 1 rat year corresponds to approximately 30 human years, the impact of senescence-related mechanisms must be considered if Gd levels in rats are assessed after very long time-intervals. In accordance with numerous other studies [54, 56–58] we evaluated Gd retention at a single, specific time point (28 days). Although this does not allow assessment of Gd retention after longer time periods, the results confirm that the elimination curve for gadoteridol from all soft tissue organs is steeper than those of other macrocyclic GBCAs. Moreover, since the measured Gd levels at 28 days after the last administration of ProHance are close to the LOQ, it is highly likely that Gd levels may not be quantifiable by validated analytical methods at later time points.

Conclusions

In conclusion, our findings confirm and extend those of Bussi et al. [12] in demonstrating considerably lower levels of retained Gd in brain and soft body tissues of rats at 28 days after the administration of ProHance at a total cumulative dose of 12 mmol/kg bodyweight than after equivalent cumulative doses of not only Dotarem and Gadovist but also the newly marketed GBCA, Clariscan™, administered under identical conditions. Furthermore, because of the lower LOQ of the ICP-MS analytical method in this study compared to that of Bussi et al. [12], we were also able to demonstrate significantly lower levels of retained Gd after ProHance in all brain and soft body tissues tested, including the skin and liver. Finally, our findings confirm that GBCA concentration and osmolarity do not influence the amount of retained Gd and show that none of the GBCAs tested have any impact on rat kidney histology, up to the tested cumulative dose.

Abbreviations

CPN: Chronic progressive nephropathy; CSF: Cerebrospinal fluid; DOTA: 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid; ECVP: European College of Veterinary Pathologists; EMA: European Medicines Agency; FDA: Food and Drug Administration; GBCA: Gadolinium-based contrast agent; ICP-MS: Inductively coupled plasma-mass spectrometry; LOQ: Limit of quantitation; WFI: Water for Injection

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Authors' contributions
SB was a major contributor in writing the manuscript. AC, RC, and AFA analyzed and interpreted the ICP-MS data. AFM contributed to the supervision of statistical analysis. AFE analyzed and interpreted computational studies results. CB peer-reviewed the histological examination of the kidney. MAK, FT, and FM were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval
The study design was reviewed and approved by the ethical committee of Charles River France as per the standard document "RatSouris_Tox subchronique_2014avril14 cea".
The study design is in general compliance with the following animal health and welfare guidelines:

- Guide for the care and use of laboratory animals, 2011.
- Decree n° 2013-118 relating to the protection of animals used in scientific experiments described in the Journal Officiel de la République Française on 01 February 2013.
- Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

Consent for publication
Not applicable

Competing interests
All authors were Bracco's employees at the time of study execution.

Author details
[1]Bracco Imaging SpA, Bracco Research Centre, Via Ribes 5, 10010 Colleretto Giacosa, TO, Italy. [2]Bracco SpA, Via Caduti di Marcinelle 13, 20134 Milano, Italy. [3]Sirius Pathology, 1705 route du Salève, 74350 Cruseilles, France. [4]Bracco Imaging SpA, Via Caduti di Marcinelle 13, 20134 Milano, Italy.

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Publisher's Note

DOSAGE AND ADMINISTRATION

Central Nervous System

ADULTS: The recommended dose of ProHance (Gadoteridol) Injection is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus (> 60 mL/min). In patients with normal renal function suspected of having poorly enhancing lesions, in the presence of negative or equivocal scans, a supplementary dose of 0.2 mmol/kg (0.4 mL/kg) may be given up to 30 minutes after the first dose.

CHILDREN (2-18 years): The recommended dose of ProHance is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min- 60 mL/min) or bolus (> 60 mL/min). The safety and efficacy of doses > 0.1 mmol/kg, and sequential and/or repeat procedures has not been studied.

Extracranial/Extraspinal Tissues

ADULTS: The recommended dose of ProHance is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus (> 60 mL/min).

CHILDREN: Safety and efficacy for extracranial/extra-spinal tissues has not been established.

Dose adjustments in renal and liver impairment have not been studied.

To ensure complete injection of the contrast medium, the injection should be followed by a 5 mL normal saline flush. The imaging procedure should be completed within 1 hour of the first injection of ProHance (Gadoteridol) Injection.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present. Any unused portion must be discarded in accordance with regulations dealing with the disposal of such materials.

HOW SUPPLIED

ProHance (Gadoteridol) Injection is a clear, colorless to slightly yellow solution containing 279.3 mg/mL of gadoteridol in rubber stoppered vials. ProHance is available in boxes of:

Five 5 mL fills in single dose 15 mL vials	(NDC 0270-1111-04)
Five 10 mL fills in single dose 30 mL vials	(NDC 0270-1111-01)
Five 15 mL fills in single dose 30 mL vials	(NDC 0270-1111-02)
Five 20 mL fills in single dose 30 mL vials	(NDC 0270-1111-03)
Five 10 mL fills in single dose 20 mL prefilled syringes	(NDC 0270-1111-16)
Five 17 mL fills in single dose 20 mL prefilled syringes	(NDC 0270-1111-45)

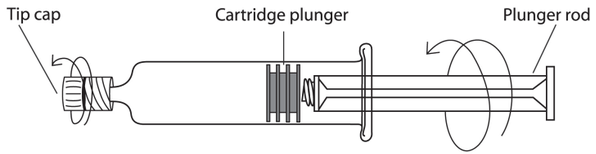
STORAGE

ProHance (Gadoteridol) Injection should be stored at 25° C (77° F) excursions permitted to 15-30° C (59-86° F) [See USP Controlled Room Temperature]. Protect from light. DO NOT FREEZE. Should freezing occur in the vial, ProHance should be brought to room temperature before use. If allowed to stand at room temperature for a minimum of 60 minutes, ProHance (Gadoteridol) Injection should return to a clear, colorless to slightly yellow solution. Before use, examine the product to assure that all solids are redissolved and that the container and closure have not been damaged. Should solids persist, discard vial. Frozen syringes should be discarded.

Directions for Use of the

ProHance® (Gadoteridol) Injection *single dose syringe**

1) Screw the threaded tip of the plunger rod clockwise into the cartridge plunger and push forward a few millimeters to break any friction between the cartridge plunger and syringe barrel.



2) Holding syringe erect, unscrew the plastic tip cap from the tip of the syringe and attach either a sterile, disposable needle or tubing with a compatible luer lock using a push-twist action.
3) Hold the syringe erect and push plunger forward until all of the air is evacuated and fluid either appears at the tip of the needle or the tubing is filled. Following the usual aspiration procedure, complete the injection. To ensure complete delivery of the contrast medium, the injection should be followed by a normal saline flush.
4) Properly dispose of the syringe and any other materials used.

*The syringe assembly is a HYPAK SCF® single dose syringe supplied by Becton Dickinson.

This product is covered by one or more of:
U.S. Patent No. 5,474,756; U.S. Patent No. 5,846,519; and U.S. Patent No. 6,143,274.

Rx Only

Manufactured for Bracco Diagnostics Inc.
Monroe Township, NJ 08831
by BIPSO GmbH - 78224 Singen (Germany)

Bracco Diagnostics

ProHance®

(Gadoteridol) Injection, 279.3 mg/mL

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

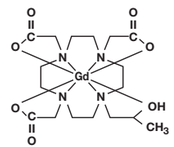
Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or**
  - **acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended ProHance dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration (see WARNINGS).**

DESCRIPTION

ProHance (Gadoteridol) Injection is a nonionic contrast medium for magnetic resonance imaging (MRI), available as a 0.5M sterile clear colorless to slightly yellow aqueous solution in vials and syringes for intravenous injection.

Gadoteridol is the gadolinium complex of 10-(2-hydroxy-propyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid with a molecular weight of 558.7, an empirical formula of $C_{17}H_{29}N_4O_7Gd$ and has the following structural formula:



Each mL of ProHance contains 279.3 mg gadoteridol, 0.23 mg calteridol calcium, 1.21 mg tromethamine and water for injection. ProHance contains no antimicrobial preservative.

ProHance has a pH of 6.5 to 8.0. Pertinent physicochemical data are noted below:

PARAMETER	
Osmolality (mOsmol/kg water) @ 37° C	630
Viscosity (cP) @ 20° C	2.0
@ 37° C	1.3
Specific Gravity @ 25° C	1.140
Density (g/mL) @ 25° C	1.137
Octanol: H_2O coefficient	-3.68 ± 0.02

ProHance has an osmolality 2.2 times that of plasma (285 mOsmol/kg water) and is hypertonic under conditions of use.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of intravenously administered gadoteridol in normal subjects conforms to a two-compartment open model with mean distribution and elimination half-lives (reported as mean ± SD) of about 0.20 ± 0.04 hours and 1.57 ± 0.08 hours, respectively.

Gadoteridol is eliminated in the urine with 94.4 ± 4.8% (mean ± SD) of the dose excreted within 24 hours post-injection. It is unknown if biotransformation or decomposition of gadoteridol occur *in vivo*.

The renal and plasma clearance rates (1.41 ± 0.33 mL/ min/kg and 1.50 ± 0.35 mL/min/kg, respectively) of gadoteridol are essentially identical, indicating no alteration in elimination kinetics on passage through the kidneys and that the drug is essentially cleared through the kidney. The volume of distribution (204 ± 58 mL/kg) is equal to that of extracellular water, and clearance is similar to that of substances which are subject to glomerular filtration. Following GBCA administration, gadolinium is present for months or years in brain, bone, skin, and other organs (See **WARNINGS-Gadolinium Retention**).

It is unknown if protein binding of ProHance occurs *in vivo*.

Pharmacodynamics

Gadoteridol is a paramagnetic agent and, as such, develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by the paramagnetic agent results in a relatively large local magnetic field, which can enhance the relaxation rates of water protons in the vicinity of the paramagnetic agent.

In magnetic resonance imaging (MRI), visualization of normal and pathologic brain 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, gadoteridol decreases T1 relaxation times in the target tissues. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

Disruption of the blood-brain barrier or abnormal vascularity allows accumulation of gadoteridol in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetics of ProHance in various lesions is not known.

CLINICAL TRIALS

ProHance was evaluated in two blinded read trials in a total of 133 adults who had an indication for head and neck extracranial or extraspinal magnetic resonance imaging. These 133 adults (74 men, 59 women) had a mean age of 53 with a range of 19 to 76 years. Of these patients, 85% were Caucasian, 13% Black, 2% Asian, and < 1% other. The results of the non-contrast and gadoteridol MRI scans were compared. In this database, approximately 75-82% of the scans were enhanced. 45-48% of the scans provided additional diagnostic information, and 8-25% of the diagnoses were changed. The relevance of the findings to disease sensitivity and specificity has not been fully evaluated.

ProHance was evaluated in a multicenter clinical trial of 103 children who had an indication for a brain or spine MRI. These 103 children, (54 boys and

49 girls) had a mean age of 8.7 years with an age range of 2 to 20 years. Of these 103 children, 54 were between 2 and 12 years of age. Also, of these 103 children, 74% were Caucasian, 11% Black, 12% Hispanic, 2% Asian, and 2% other. The results of the non-contrast and gadoteridol MRI scans were compared. ProHance was given in one single 0.1 mmol/kg dose. Repeat dosing was not studied. In this database, MRI enhancement was noted in approximately 60% of the scans and additional diagnostic information in 30-95% of the scans.

INDICATIONS AND USAGE

Central Nervous System

ProHance (Gadoteridol) Injection is indicated for use in MRI in adults and children over 2 years of age to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues.

Extracranial/Extraspinal Tissues

ProHance is indicated for use in MRI in adults to visualize lesions in the head and neck.

CONTRAINDICATIONS

ProHance is contraindicated in patients with known allergic or hypersensitivity reactions to ProHance (see **WARNINGS**).

WARNINGS

Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30-59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60-89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following ProHance administration to Bracco Diagnostics (1-800-257-5181) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended ProHance dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Acute Kidney Injury (AKI)

In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.

Hypersensitivity Reactions

Severe and fatal hypersensitivity reactions including anaphylaxis have been observed with administration of gadolinium products, including ProHance. Patients with a history of allergy, drug reactions or other hypersensitivity-like disorders should be closely observed during the procedure and for several hours after drug administration. If a reaction occurs, stop ProHance and immediately begin appropriate therapy including resuscitation. (See **PRECAUTIONS - General**)

Deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by ProHance may possibly potentiate sickle erythrocyte alignment. ProHance in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of ProHance to exclude the possibility of increased hemolysis.

Gadolinium Retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver, and spleen. The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) and Optimark (gadoversetamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Dotarem (gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol)].

Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function (See **WARNINGS-Nephrogenic Systemic Fibrosis**). There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention (See **ADVERSE REACTIONS**).

While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible.

PRECAUTIONS

General

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

Personnel trained in resuscitation techniques and resuscitation equipment should be available.

The possibility of a reaction, including serious, life threatening, or fatal, anaphylactic or cardiovascular reactions, or other idiosyncratic reactions (see **ADVERSE REACTIONS**), should always be considered, especially in those patients with a history of a known clinical hypersensitivity or a history of asthma or other allergic respiratory disorders.

Gadoteridol is cleared from the body by glomerular filtration. The hepato-biliary enteric pathway of excretion has not been demonstrated with ProHance. Dose adjustments in renal or hepatic impairment have not been studied. Therefore, caution should be exercised in patients with either renal or hepatic impairment.

In a patient with a history of grand mal seizure, the possibility to induce such a seizure by ProHance is unknown.

When ProHance (Gadoteridol) Injection is to be injected using nondisposable equipment, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. After ProHance is drawn into a syringe, the solution should be used immediately.

Repeat Procedures: Repeated procedures have not been studied. Sequential use during the same diagnostic session has only been studied in central nervous system use. (See **Pharmacokinetics** under **CLINICAL PHARMACOLOGY** and **Central Nervous System** under **DOSAGE AND ADMINISTRATION**).

Information for patients:

General: Patients scheduled to receive ProHance should be instructed to inform their physician if the patient;

1. is pregnant or breast feeding
2. has anemia or diseases that affect the red blood cells
3. has a history of renal or hepatic disease, seizure, hemoglobinopathies, asthma or allergic respiratory diseases
4. has recently received a GBCA.

Nephrogenic Systemic Fibrosis: GBCAs increase the risk for NSF among patients with impaired elimination of the drugs. To counsel patients at risk for NSF:

- Describe the clinical manifestations of NSF
- Describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following ProHance administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

Gadolinium Retention: Advise patients that gadolinium is retained for months or years in brain, bone, skin, and other organs in patients with normal renal function. The clinical consequences of retention are unknown. Retention depends on multiple factors and is greater following administration of linear GBCAs than following administration of macrocyclic GBCAs. (See **WARNINGS-Gadolinium Retention**).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been performed to evaluate the carcinogenic potential of gadoteridol or potential effects on fertility.

ProHance did not demonstrate genotoxic activity in bacterial reverse mutation assays using *Salmonella typhimurium* and *Escherichia coli*, in a mouse lymphoma forward mutation assay, in an *in vitro* cytogenetic assay measuring chromosomal aberration frequencies in Chinese hamster ovary cells, nor in an *in vivo* mouse micronucleus assay at intravenous doses up to 5.0 mmol/kg.

Pregnancy

GBCAs cross the placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive. Because of the potential risks of gadolinium to the fetus, use ProHance only if imaging is essential during pregnancy and cannot be delayed.

Contrast enhancement is visualized in the human placenta and fetal tissues after maternal GBCA administration.

Cohort studies and case reports on exposure to GBCAs during pregnancy have not reported a clear association between GBCAs and adverse effects in the exposed neonates. However, a retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. Limitations of this study include a lack of comparison with non-contrast MRI and lack of information about the maternal indication for MRI. Overall, these data preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of GBCAs in pregnancy.

GBCAs administered to pregnant non-human primates (0.1 mmol/kg on gestational days 85 and 135) result in measurable gadolinium concentration in the offspring in bone, brain, skin, liver, kidney, and spleen for at least 7 months. GBCAs administered to pregnant mice (2 mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one month postnatal age.

ProHance administered to rats at 10 mmol/kg/day (33 times the maximum recommended human dose of 0.3 mmol/kg or 6 times the human dose based on a mmol/m^2 comparison) for 12 days during gestation doubled the incidence of postimplantation loss. When rats were administered 6.0 or 10.0 mmol/ kg/day for 12 days, an increase in spontaneous locomotor activity was observed in the offspring. ProHance increased the incidence of spontaneous abortion and early delivery in rabbits administered 6 mmol/kg/day (20 times the maximum recommended human dose or 7 times the human dose based on a mmol/m^2 comparison) for 13 days during gestation.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ProHance is administered to a nursing woman.

Pediatric Use

Safety and efficacy in children under the age of 2 years have not been established. The safety and efficacy of doses > 0.1 mmol/kg; and sequential and/or repeat procedures has not been studied in children. (See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections)

ADVERSE REACTIONS

The adverse events described in this section were observed in clinical trials involving 1251 patients (670 males and 581 females). Adult patients ranged in age from 18-91 yrs. Pediatric patients ranged from 2-17 years. The racial breakdown was 83% Caucasian, 8% Black, 3% Hispanic, 2% Asian, and 1% other. In 2% of the patients, race was not reported.

The most commonly noted adverse experiences were nausea and taste perversion with an incidence of 1.4%. These events were mild to moderate in severity.

The following additional adverse events occurred in fewer than 1% of the patients:

Body as a Whole:	Facial Edema; Neck Rigidity; Pain; Pain at Injection Site; Injection Site Reaction; Chest Pain; Headache; Fever; Itching; Watery Eyes; Abdominal Cramps; Tingling Sensation in Throat; Laryngismus; Flushed Feeling; Vasovagal Reaction; Anaphylactoid Reactions (characterized by cardiovascular, respiratory and cutaneous symptoms)
Cardiovascular:	Prolonged P-R Interval; Hypotension; Elevated Heart Rate; A-V Nodal Rhythm
Digestive:	Edematous and/or itching tongue; Gingivitis; Dry Mouth; Loose Bowel; Vomiting
Nervous System:	Anxiety; Dizziness; Paresthesia; Mental Status Decline; Loss of Coordination in Arm; Staring Episode; Seizure; Syncope
Respiratory System:	Dyspnea; Rhinitis; Cough.
Skin and Appendages:	Pruritus; Rash; Rash Macular Papular; Urticaria; Hives; Tingling Sensation of Extremity and Digits
Special Senses:	Tinnitus

The following adverse drug reactions have also been reported:

General Disorders and Administration Site Conditions:	Adverse events with variable onset and duration have been reported after GBCA administration (See **WARNINGS-Gadolinium Retention**). These include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems.
Body as a Whole:	Generalized Edema; Laryngeal Edema; Malaise; Anaphylactoid Reactions (characterized by cardiovascular, respiratory and cutaneous symptoms, and rarely resulting in Death).
Cardiovascular:	Cardiac Arrest; Bradycardia; Hypertension; and Death in association with pre-existing cardiovascular disorders.
Digestive:	Increased Salivation; Dysphagia
Nervous System:	Stupor; Tremor; Loss of Consciousness
Respiratory:	Apnea; Wheezing
Skin and Appendages:	Gadolinium associated plaques; Sweating; and Cyanosis
Special Senses:	Voice Alteration; transitory deafness
Urogenital:	Urinary Incontinence

OVERDOSAGE

Clinical consequences of overdose with ProHance have not been reported.

MEDICATION GUIDE
PROHANCE® *(prō-ˈhan(t)s)*
(Gadoteridol)
Injection for intravenous use

What is PROHANCE?

- PROHANCE is a prescription medicine called a gadolinium-based contrast agent (GBCA). PROHANCE, like other GBCAs, is used with a magnetic resonance imaging (MRI) scanner.
- An MRI exam with a GBCA, including PROHANCE, helps your doctor to see problems better than an MRI exam without a GBCA.
- Your doctor has reviewed your medical records and has determined that you would benefit from using a GBCA with your MRI exam.

What is the most important information I should know about PROHANCE?

- PROHANCE contains a metal called gadolinium. Small amounts of gadolinium can stay in your body including the brain, bones, skin and other parts of your body for a long time (several months to years).
- It is not known how gadolinium may affect you, but so far, studies have not found harmful effects in patients with normal kidneys.
- Rarely, patients have reported pains, tiredness, and skin, muscle or bone ailments for a long time, but these symptoms have not been directly linked to gadolinium.
- There are different GBCAs that can be used for your MRI exam. The amount of gadolinium that stays in the body is different for different gadolinium medicines. Gadolinium stays in the body more after Omniscan or Optimark than after Eovist, Magnevist, or MultiHance. Gadolinium stays in the body the least after Dotarem, Gadavist, or ProHance.
- People who get many doses of gadolinium medicines, women who are pregnant and young children may be at increased risk from gadolinium staying in the body.
- Some people with kidney problems who get gadolinium medicines can develop a condition with severe thickening of the skin, muscles and other organs in the body (nephrogenic systemic fibrosis). Your healthcare provider should screen you to see how well your kidneys are working before you receive PROHANCE.

Do not receive PROHANCE if you have had a severe allergic reaction to PROHANCE.

Before receiving PROHANCE, tell your healthcare provider about all your medical conditions, including if you:

- have had any MRI procedures in the past where you received a GBCA. Your healthcare provider may ask you for more information including the dates of these MRI procedures.
- are pregnant or plan to become pregnant. It is not known if PROHANCE can harm your unborn baby. Talk to your healthcare provider about the possible risks to an unborn baby if a GBCA such as PROHANCE is received during pregnancy
- have kidney problems, diabetes, or high blood pressure
- have had an allergic reaction to dyes (contrast agents) including GBCAs

What are the possible side effects of PROHANCE?

- **See "What is the most important information I should know about PROHANCE?"**
- **Allergic reactions. PROHANCE can cause allergic reactions that can sometimes be serious. Your healthcare provider will monitor you closely for symptoms of an allergic reaction.**

The most common side effects of PROHANCE include: nausea, taste perversion, headache, feeling hot, or burning at the injection site.

These are not all the possible side effects of PROHANCE.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of PROHANCE.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider for information about PROHANCE that is written for health professionals.

What are the ingredients in PROHANCE?

Active ingredient: gadoteridol

Inactive ingredients: calteridol calcium, tromethamine

Manufactured by: BIPSO GmbH-78224 Singen (Germany)

Manufactured for: Bracco Diagnostics Inc., Monroe Township, NJ 08831

US Patent No. 5,474,756; 5,846,519; and 6,143,274.

For more information, go to www.imaging.bracco.com or call 1-800-257-5181.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 04/2018

COEB503

Bracco Diagnostics

multihance®

(gadobenate dimeglumine) injection, 529 mg/mL

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MultiHance safely and effectively. See full prescribing information for MultiHance.

MultiHance (gadobenate dimeglumine) Injection

Initial U.S. Approval: 2004

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

See full prescribing information for complete boxed warning

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- **The risk for NSF appears highest among patients with:**
  - **chronic, severe kidney disease (GFR <30 mL/ min/1.73m^2), or**
  - **acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing. (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, MRI of the Central Nervous System (1.1)	01/2018
Warnings and Precautions, Gadolinium Retention (5.3)	04/2018

----------INDICATIONS AND USAGE----------

- magnetic resonance imaging (MRI) of the central nervous system (CNS) in adults and pediatric patients (including term neonates), to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine, and associated tissues (1.1)
- magnetic resonance angiography (MRA) to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease. (1.2)

---------DOSAGE AND ADMINISTRATION---------

- The recommended dose of MultiHance is 0.2 mL/kg (0.1 mmol/kg) administered as a rapid bolus intravenous injection.
- For MRI of the CNS in pediatric patients below 2 years of age the recommended dosage range is 0.1 to 0.2 mL/kg.
- To ensure complete injection of the contrast medium, follow the injection with a saline flush of at least 5 mL in MRI of the CNS and at least 20 mL in MRA. (2)

---------DOSAGE FORMS AND STRENGTHS---------

Each mL of MultiHance Injection contains 529 mg gadobenate dimeglumine and is available in single use vials. (3)

----------CONTRAINDICATIONS----------

MultiHance is contraindicated in patients with known allergic or hypersensitivity reactions to gadolinium-based contrast agents. (4)

---------WARNINGS AND PRECAUTIONS---------

- Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeated dosing appears to increase the risk (5.1)
- Hypersensitivity: anaphylactic/anaphylactoid reactions with cardiovascular, respiratory and cutaneous manifestations, ranging from mild to severe reactions including shock can occur. Monitor patients closely for need of emergency cardiorespiratory support. (5.2)
- Gadolinium is retained for months or years in brain, bone, and other organs. (5.3)

----------ADVERSE REACTIONS----------

The most commonly reported adverse reactions are nausea (1.3%) and headache (1.2%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bracco Diagnostics Inc at 1-800-257-5181 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------USE IN SPECIFIC POPULATIONS---------

Pregnancy: Use only if imaging is essential during pregnancy and cannot be delayed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 08/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs.
Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or**
  - **acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended MultiHance dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration. [see *Warnings and Precautions (5.1)*]**

1 INDICATIONS AND USAGE

1.1 MRI of the Central Nervous System (CNS)

MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the central nervous system (CNS) in adults and pediatric patients (including term neonates), to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

1.2 MRA of Renal and Aorto-ilio-femoral Vessels

MultiHance is indicated for use in magnetic resonance angiography (MRA) to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Imaging Instructions

2.1.1 MRI of the CNS

In adults and in pediatric patients over 2 years of age, the recommended dose of MultiHance for MRI of the CNS is 0.2 mL/kg (0.1 mmol/kg) administered as a rapid bolus intravenous injection. In pediatric patients below 2 years of age, the recommended dosage range is 0.1 to 0.2 mL/kg administered as a rapid bolus intravenous injection. To ensure complete injection of the contrast medium, follow the injection with a saline flush of at least 5 mL. Imaging of the CNS can be performed starting immediately after the bolus injection of MultiHance.

2.1.2 MRA of Renal and Aorto-ilio-femoral Vessels

For MRA examination, the recommended dose is 0.2 mL/kg (0.1 mmol/kg) administered as a rapid bolus intravenous injection followed by at least 20 mL saline flush either manually or using an automatic injector system. Start imaging immediately after the administration of MultiHance, with scan delay calculated by test bolus or automatic bolus detection technique. If an automatic contrast detection pulse sequence is not used for bolus timing, then a test bolus injection of 1-2 mL of MultiHance should be used to calculate the appropriate scan delay.

2.2 Dosing Table

TABLE 1: WEIGHT-BASED DOSING VOLUMES FOR: CNS IMAGING (ADULTS AND PEDIATRICS ≥ 2 YEARS OF AGE*) AND MRA IMAGING (ADULTS ONLY)

		0.1mM/kg dose
Kilograms (Kg)	Pounds (lb)	Volume, Milliliters (mL)
2.5	5.5	0.5
5	11	1.0
10	22	2.0
15	33	3.0
20	44	4.0
25	55	5.0
30	66	6.0
35	77	7.0
40	88	8.0
45	99	9.0
50	110	10.0
55	121	11.0
60	132	12.0
65	143	13.0
70	154	14.0
75	165	15.0
80	176	16.0
85	187	17.0
90	198	18.0
95	209	19.0
100	220	20.0
105	231	21.0
110	242	22.0
115	253	23.0
120	264	24.0
125	275	25.0
130	286	26.0
135	297	27.0
140	308	28.0
145	319	29.0
150	330	30.0

*For pediatric patients less than 2 years of age, one-half of the per kg dose may be used.

2.3 Administration

Inspect the MultiHance vial visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present. Draw MultiHance into a syringe and inject using sterile technique.

Do not mix intravenous medications or parenteral nutrition solutions with MultiHance. Do not administer other medications in the same intravenous line with MultiHance.

MultiHance vials are intended for single use only. Administer immediately after opening and discard any unused product.

3 DOSAGE FORMS AND STRENGTHS

MultiHance is a sterile, nonpyrogenic, clear, colorless to slightly yellow aqueous solution for intravenous use only, containing 529 mg gadobenate dimeglumine per mL.

4 CONTRAINDICATIONS

MultiHance is contraindicated in patients with known allergic or hypersensitivity reactions to gadolinium-based contrast agents [see ***Warnings and Precautions (5.2)***].

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30-59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60-89 mL/min/1.73m^2).

NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following MultiHance administration to Bracco Diagnostics (1-800-257-5181) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended MultiHance dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown [see ***Dosage and Administration (2)*** and ***Clinical Pharmacology (12)***].

5.2 Hypersensitivity Reactions

Anaphylactic and anaphylactoid reactions have been reported, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of MultiHance administration and resolved with prompt emergency treatment. Prior to MultiHance administration, ensure the availability of personnel trained and medications to treat hypersensitivity reactions. If such a reaction occurs stop MultiHance and immediately begin appropriate therapy. Additionally, consider the risk for hypersensitivity reactions, especially in patients with a history of hypersensitivity reactions or a history of asthma or other allergic disorders. Observe patients for signs and symptoms of a hypersensitivity reaction during and for up to 2 hours after MultiHance administration.

5.3 Gadolinium Retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver, and spleen. The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) and Optimark (gadoversetamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Dotarem (gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol)].

Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function [see ***Warnings and Precautions (5.1)***]. There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention [see ***Adverse Reactions (6.2)***]. While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible.

5.4 Acute Renal Failure

In patients with renal insufficiency, acute renal failure requiring dialysis or worsening renal function have occurred with the use of gadolinium-based contrast agents. The risk of renal failure may increase with increasing dose of the contrast agent. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. Consider follow-up renal function assessments for patients with a history of renal dysfunction.

5.5 Extravasation and Injection Site Reactions

Extravasation of MultiHance may lead to injection site reactions, characterized by local pain or burning sensation, swelling, blistering, and necrosis. In animal experiments, local reactions including eschar and necrosis were noted even on Day 8 post perivenous injection of MultiHance. Exercise caution to avoid local extravasation during intravenous administration of MultiHance. If extravasation occurs, evaluate and treat as necessary if local reactions develop.

5.6 Cardiac Arrhythmias

Cardiac arrhythmias have been observed in patients receiving MultiHance in clinical trials [see ***Adverse Reactions (6.1)***]. Assess patients for underlying conditions or medications that predispose to arrhythmias.

A double-blind, placebo-controlled, 24-hour post dose continuous monitoring, crossover study in 47 subjects evaluated the effect of 0.2 mmol/kg MultiHance on ECG intervals, including QTc. The average changes in QTc values compared with placebo were minimal (<5 msec). QTc prolongation between 30 and 60 msec were noted in 20 subjects who received MultiHance vs. 11 subjects who received placebo. Prolongations ≥61 msec were noted in 6 subjects who received MultiHance and in 3 subjects who received placebo. None of these subjects had associated malignant arrhythmias. The effects on QTc by MultiHance dose, other drugs, and medical conditions were not systematically studied.

5.7 Interference with Visualization of Certain Lesions

Certain lesions seen on non-contrast images may not be seen on contrast-images. Exercise caution when interpreting contrast MR images in the absence of companion non-contrast MR images.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Nephrogenic systemic fibrosis [see ***Warnings and Precautions (5.1)***]
- Hypersensitivity reactions [see ***Warnings and Precautions (5.2)***]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult

In clinical trials with MultiHance, a total of 4967 adult subjects (137 healthy volunteers and 4830 patients) received MultiHance at doses ranging from 0.005 to 0.4 mmol/kg. There were 2838 (57%) men and 2129 (43%) women with a mean age of 56.5 years (range 18 to 93 years). A total of 4403 (89%) subjects were Caucasian, 134 (3%) Black, 275 (6%) Asian, 40 (1%) Hispanic, 70 (1%) in other racial groups, and for 45 (1%) subjects, race was not reported.

The most commonly reported adverse reactions in adult subjects who received MultiHance were nausea (1.3%) and headache (1.2%). Most adverse reactions were mild to moderate in intensity. One subject experienced a serious anaphylactoid reaction with laryngeal spasm and dyspnea [see ***Warnings and Precautions (5.2)***]. Serious adverse reactions consisting of convulsions, pulmonary edema, acute necrotizing pancreatitis, and anaphylactoid reactions were reported in 0.1% of subjects in clinical trials.

Adverse reactions that occurred in at least 0.5% of 4967 adult subjects who received MultiHance are listed below (Table 2), in decreasing order of occurrence within each system.

TABLE 2: ADVERSE REACTIONS REPORTED IN ≥0.5% OF ADULT SUBJECTS WHO RECEIVED MULTIHANCE IN CLINICAL TRIALS

Number of subjects dosed	4967
Number of subjects with any adverse reaction	517 (10.4%)
Gastrointestinal Disorders	
Nausea	67 (1.3%)
General Disorders and Administration Site Disorders	
Injection Site Reaction	54 (1.1%)
Feeling Hot	49 (1.0%)
Nervous System Disorders	
Headache	60 (1.2%)
Dysgeusia	33 (0.7%)
Paresthesia	24 (0.5%)
Dizziness	24 (0.5%)

The following adverse reactions occurred in less than 0.5% of the 4967 adult subjects who received MultiHance. Serious adverse reactions described above are not repeated below.

Blood and Lymphatic System Disorders: Basophilia;
Cardiac Disorders: Atrioventricular block first degree;
Eye Disorders: Eye pruritus, eye swelling, ocular hyperemia, visual disturbance;
Gastrointestinal Disorders: Abdominal pain or discomfort, diarrhea, dry mouth, lip swelling, paraesthesia oral, tongue edema, vomiting;
General Disorders and Administration Site Conditions: Chest pain or discomfort, chills, malaise;
Immune System Disorders: Hypersensitivity;
Investigations: Nonspecific changes in laboratory tests (including hematology, blood chemistry, liver enzymes and urinalysis), blood pressure and electrocardiogram parameters (including PR, QRS and QT intervals and ST-T segment changes).
Musculoskeletal and Connective Tissue Disorders: Myalgia;
Nervous System Disorders: Parosmia, tremor;
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, laryngospasm, nasal congestion, sneezing, wheezing;
Skin and Subcutaneous Tissue Disorders: Hyperhidrosis, pruritus, rash, swelling face, urticaria.

Pediatric Patients

In clinical trials of MultiHance in MRI of the CNS, 307 pediatric subjects received MultiHance at a dose of 0.1 mmol/kg. A total of 160 (52%) subjects were male and the overall mean age was 6.0 years (range, 2 days to 17 years). A total of 211 (69%) subjects were Caucasian, 24 (8%) Black, 15 (5%) Asian, 39 (13%), Hispanic, 2 (<1%) in other racial groups, and for 16 (5%), race was not reported.

Adverse reactions were reported for 14 (4.6%) of the subjects. The frequency and the nature of the adverse reactions were similar to those seen in the adult patients. The most commonly reported adverse reactions were vomiting (1.0%), pyrexia (0.7%), and hyperhidrosis (0.7%). No subject died during study participation.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of MultiHance. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Anaphylactic, anaphylactoid and hypersensitivity reactions manifested with various degrees of severity up to anaphylactic shock, loss of consciousness and death. The reactions generally involved signs or symptoms of respiratory, cardiovascular, and/or mucocutaneous abnormalities.
General Disorders and Administration Site Conditions: Extravasation of MultiHance may lead to injection site reactions, characterized by local pain or burning sensation, swelling, blistering, and necrosis [see ***Warnings and Precautions (5.4)***]. Adverse events with variable onset and duration have been reported after GBCA administration [see ***Warnings and Precautions (5.3)***]. These include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems.
Skin: Gadolinium associated plaques.

7 DRUG INTERACTIONS

7.1 Transporter-Based Drug-Drug Interactions

MultiHance and other drugs may compete for the canalicular multispecific organic anion transporter (MOAT also referred to as MRP2 or ABCC2). Therefore MultiHance may prolong the systemic exposure of drugs such as cisplatin, anthracyclines (e.g. doxorubicin, daunorubicin), vinca alkaloids (e.g. vincristine), methotrexate, etoposide, tamoxifen, and paclitaxel. In particular, consider the potential for prolonged drug exposure in patients with decreased MOAT activity (e.g. Dubin Johnson syndrome).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

GBCAs cross the placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive *(see Data)*. In animal reproduction studies,

gadobenate dimeglumine has been shown to be teratogenic in rabbits following repeated intravenous administration during organogenesis at doses up to 6 times the recommended human dose. There were no adverse developmental effects observed in rats with intravenous administration of gadobenate dimeglumine during organogenesis at doses up to three times the recommended human dose *(see Data)*. Because of the potential risks of gadolinium to the fetus, use MultiHance only if imaging is essential during pregnancy and cannot be delayed.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and is 15 to 20%, respectively.

Data

Human Data

Contrast enhancement is visualized in the human placenta and fetal tissues after maternal GBCA administration. Cohort studies and case reports on exposure to GBCAs during pregnancy have not reported a clear association between GBCAs and adverse effects in the exposed neonates. However, a retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. Limitations of this study include a lack of comparison with non-contrast MRI and lack of information about the maternal indication for MRI. Overall, these data preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of GBCAs in pregnancy.

Animal Data

Gadolinium Retention

GBCAs administered to pregnant non-human primates (0.1 mmol/kg on gestational days 85 and 135) result in measurable gadolinium concentration in the offspring in bone, brain, skin, liver, kidney, and spleen for at least 7 months. GBCAs administered to pregnant mice (2 mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one month postnatal age.

Reproductive Toxicology

Gadobenate dimeglumine has been shown to be teratogenic in rabbits when administered intravenously at 2 mmol/kg/day (6 times the recommended human dose based on body surface area) during organogenesis (day 6 to 18) inducing microphthalmia/small eye and/or focal retinal fold in 3 fetuses from 3 separate litters. In addition, MultiHance intravenously administered at 3 mmol/kg/day (10 times the recommended human dose based on body surface area) has been shown to increase intrauterine deaths in rabbits. There was no evidence that MultiHance induced teratogenic effects in rats at doses up to 2 mmol/kg/day (3 times the recommended human dose based on body surface area), however, rat dams exhibited no systemic toxicity at this dose. There were no adverse effects on the birth, survival, growth, development and fertility of the F1 generation at doses up to 2 mmol/kg in a rat peri- and post-natal (Segment III) study.

8.2 Lactation

Risk Summary

Limited literature reports that breastfeeding after gadobenate dimeglumine administration to the mother would result in the infant receiving an oral dose of 0.001%-0.04% of the maternal dose. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Additionally, there is limited GBCA gastrointestinal absorption. The developmental and health benefits of breastfeeding should be considered together with the mother's clinical need for MultiHance and any potential adverse effects on the breastfed infant from MultiHance or from the underlying maternal condition.

8.4 Pediatric Use

MultiHance is approved for intravenous use for MRI of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues in pediatric patients from birth, including term neonates, to less than 17 years of age. Pediatric use is based on evidence of effectiveness in adults and in 202 pediatric patients 2 years of age and older, in addition to experience in 105 pediatric patients birth to less than 2 years of age that supported extrapolation from adult data [see ***Clinical Studies (14)***]. Adverse reactions in pediatric patients were similar to those reported in adults [see ***Adverse Reactions (6.1)***]. No dose adjustment according to age is necessary in pediatric patients two years of age and older. For pediatric patients, less than 2 years of age, the recommended dosage range is 0.1 to 0.2 mL/kg [see ***Dosage and Administration (2.1), Pharmacokinetics (12.3)***]. The safety of MultiHance has not been established in preterm neonates.

8.5 Geriatric Use

Of the total number of 4967 adult subjects in clinical studies of MultiHance, 33% were 65 and over. No overall differences in safety or effectiveness were observed between these elderly subjects and the younger subjects. The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to MultiHance may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function it may be useful to monitor renal function.

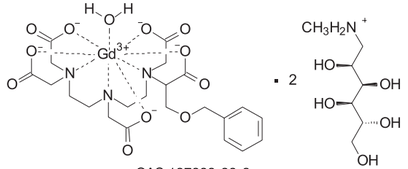
10 OVERDOSAGE

Clinical consequences of overdosage with MultiHance have not been reported. Treatment of an overdosage should be directed toward support of vital functions and prompt institution of symptomatic therapy. In a Phase 1 clinical study, doses up to 0.4 mmol/kg were administered to patients. MultiHance has been shown to be dialyzable [see ***Clinical Pharmacology (12.3)***].

11 DESCRIPTION

MultiHance injection is supplied as a sterile, nonpyrogenic, clear, colorless to slightly yellow aqueous solution intended for intravenous use only. Each mL of MultiHance contains 529 mg gadobenate dimeglumine and water for injection. MultiHance contains no preservatives.

Gadobenate dimeglumine is chemically designated as (4RS)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)] gadolinate(2-) dihydrogen compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2) with a molecular weight of 1058.2 and an empirical formula of $C_{22}H_{28}GdN_3O_{11} \bullet 2C_7H_{17}NO_5$. The structural formula is as follows:



CAS 127000-20-8

MultiHance has a pH of 6.5-7.5. Pertinent physicochemical parameters are provided below:

Osmolality	1.970 osmol/kg @ 37°C
Viscosity	5.3 mPas @ 37°C
Density	1.220 g/mL @ 20°C

MultiHance has an osmolality 6.9 times that of plasma (285 mOsmol/kg water) and is hypertonic under conditions of use.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gadobenate dimeglumine is a paramagnetic agent and, as such, develops a magnetic moment when placed in a magnetic field. The large magnetic moment produced by the paramagnetic agent results in a large local magnetic field, which can enhance the relaxation rates of water protons in its vicinity leading to an increase of signal intensity (brightness) of 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, gadobenate dimeglumine decreases the T1 and T2 relaxation time in target tissues. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

12.2 Pharmacodynamics

Unlike other tested paramagnetic contrast agents (See Table 3), MultiHance demonstrates weak and transient interactions with serum proteins that causes slowing in the molecular tumbling dynamics, resulting in strong increases in relaxivity in solutions containing serum proteins. The improved relaxation effect can contribute to increased contrast-to-noise ratio and lesion-to-brain ratio, which may improve visualization.

TABLE 3: RELAXIVITY ($mM^{-1}s^{-1}$) OF GADOLINIUM CHELATES

	Human plasma	
	r_1	r_2
Gadobenate	9.7[1]	12.5[1]
Gadopentetate	4.9[1]	6.3[1]
Gadodiamide	5.4[2]	--
Gadoteridol	5.4[2]	--

r_1 and r_2 relaxivities indicate the efficiency in shortening T1 and T2 relaxation times, respectively.
[1] In heparinized human plasma, at 39°C.
[2] In citrated human plasma, at 37°C.
-- Not available

Disruption of the blood-brain barrier or abnormal vascularity allows enhancement by MultiHance of lesions such as neoplasms, abscesses, and infarcts. Uptake of MultiHance into hepatocytes has been demonstrated.

12.3 Pharmacokinetics

Three single-dose intravenous studies were conducted in 32 healthy male subjects to assess the pharmacokinetics of gadobenate dimeglumine. The doses administered in these studies ranged from 0.005 to 0.4 mmol/kg. Upon injection, the meglumine salt is completely dissociated from the gadobenate dimeglumine complex. Thus, the pharmacokinetics is based on the assay of gadobenate ion, the MRI contrast effective ion in gadobenate dimeglumine. Data for plasma concentration and area under the curve demonstrated linear dependence on the administered dose. The pharmacokinetics of gadobenate ion following intravenous administration can be best described using a two-compartment model.

Distribution

Gadobenate ion has a rapid distribution half-life (reported as mean ± SD) of 0.084 ± 0.012 to 0.605 ± 0.072 hours. Volume of distribution of the central compartment ranged from 0.074 ± 0.017 to 0.158 ± 0.038 L/kg, and estimates of volume of distribution by area ranged from 0.170 ± 0.016 to 0.282 ± 0.079 L/kg. These latter estimates are approximately equivalent to the average volume of extracellular body water in man. *In vitro* studies showed no appreciable binding of gadobenate ion to human serum proteins. Following GBCA administration, gadolinium is present for months or years in brain, bone, skin, and other organs [see ***Warnings and Precautions (5.3)***].

Elimination

Gadobenate ion is eliminated predominately via the kidneys, with 78% to 96% of an administered dose recovered in the urine. Total plasma clearance and renal clearance estimates of gadobenate ion were similar, ranging from 0.093 ± 0.010 to 0.133 ± 0.270 L/hr/kg and 0.082 ± 0.007 to 0.104 ± 0.039 L/hr/kg, respectively. The clearance is similar to that of substances that are subject to glomerular filtration.

The mean elimination half-life ranged from 1.17 ± 0.26 to 2.02 ± 0.60 hours. A small percentage of the administered dose (0.6% to 4%) is eliminated via the biliary route and recovered in feces.

Metabolism

There was no detectable biotransformation of gadobenate ion. Dissociation of gadobenate ion *in vivo* has been shown to be minimal, with less than 1% of the free chelating agent being recovered alone in feces.

Pharmacokinetics in Special Populations

Renal Impairment: A single intravenous dose of 0.2 mmol/kg of MultiHance was administered to 20 subjects with impaired renal function (6 men and 3 women with moderate renal impairment [urine creatinine clearance >30 to <60 mL/min] and 5 men and 6 women with severe renal impairment [urine creatinine clearance >10 to <30 mL/min]). Mean estimates of the elimination half-life were 6.1 ± 3.0 and 9.5 ± 3.1 hours for the moderate and severe renal impairment groups, respectively as compared with 1.0 to 2.0 hours in healthy volunteers.

Hemodialysis: A single intravenous dose of 0.2 mmol/kg of MultiHance was administered to 11 subjects (5 males and 6 females) with end-stage renal disease requiring hemodialysis to determine the pharmacokinetics and dialyzability of gadobenate. Approximately 72% of the dose was recovered by hemodialysis over a 4-hour period. The mean elimination half-life on dialysis was 1.21 ± 0.29 hours as compared with 42.4 ± 24.4 hours when off dialysis.

Hepatic Impairment: A single intravenous dose of 0.1 mmol/kg of MultiHance was administered to 11 subjects (8 males and 3 females) with impaired liver function (Class B or C modified Child-Pugh Classification). Hepatic impairment had little effect on the pharmacokinetics of MultiHance with the parameters being similar to those calculated for healthy subjects.

Gender, Age, Race: A multiple regression analysis performed using pooled data from several pharmacokinetic studies found no significant effect of sex upon the pharmacokinetics of gadobenate. Clearance appeared to decrease slightly with increasing age. Since variations due to age appeared marginal, dosage adjustment for geriatric population is not recommended. Pharmacokinetic differences due to race have not been systematically studied.

Pediatric: A population pharmacokinetic analysis incorporated data from 25 healthy subjects (14 males and 11 females) and 15 subjects undergoing MR imaging of the central nervous system (7 males and 8 females) between ages of 2 and 16 years. The subjects received a single intravenous dose of 0.1 mmol/kg of MultiHance. The geometric mean C_{max} was 62.3 µg/mL (n=16) in children 2 to 5 years of age, and 64.2 µg/mL (n=24) in children older than 5 years. The geometric mean AUC $_{0-\infty}$ was 77.9 µg·h/mL in children 2-5 years of age (n=16) and 82.6 µg·h/mL in children older than 5 years (n=24). The geometric mean half-life was 1.2 hours in children 2 to 5 years of age and 0.93 hours in children older than 5 years. There was no significant gender-related difference in the pharmacokinetic parameters in the pediatric patients. Over 80% of the dose was recovered in urine after 24 hours. Pharmacokinetic simulations indicate similar AUC and C_{max} values for MultiHance in pediatric subjects less than 2 years when compared to those reported for adults; no age-based dose adjustment is necessary for this pediatric population.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of MultiHance.

The results for MultiHance were negative in the following genetic toxicity studies: 1) *in vitro* bacteria reverse mutation assays, 2) an *in vitro* gene mutation assay in mammalian cells, 3) an *in vitro* chromosomal aberration assay, 4) an *in vitro* unscheduled DNA synthesis assay, and 5) an *in vivo* micronucleus assay in rats.

MultiHance had no effect on fertility and reproductive performance at IV doses of up to 2 mmol/kg/day (3 times the human dose on body surface basis) for 13 weeks in male rats and for 32 days in female rats. However, vacuolation in testes and abnormal spermatogenic cells were observed when MultiHance was intravenously administered to male rats at 3 mmol/kg/day (5 times the human dose on body surface basis) for 28 days. The effects were not reversible following 28-day recovery period. The effects were not reported in dog and monkey studies (at doses up to about 11 and 10 times the human dose on body surface basis for dogs (28 days dosing) and monkeys (14 days dosing), respectively).

14 CLINICAL STUDIES

14.1 MRI of the CNS

Adults

MultiHance was evaluated in 426 adult patients in 2 controlled clinical trials of the central nervous system (Study A and Study B), enrolling 217 men and 209 women with a mean age of 52 years (range 18 to 88 years). The racial and ethnic representations were 88% Caucasian, 6% Black, 4% Hispanic, 1% Asian, and 1% other racial or ethnic groups. These trials were designed to compare MultiHance contrast MRI to non-contrast MRI alone. In Study A, patients highly suspected of having a lesion(s) of the CNS based on nuclear medicine imaging, computed tomography (CT), contrast CT, MRI, contrast- MRI, or angiography were randomized to receive two MRI evaluations with 0.05 mmol/kg (n=140) or 0.1 mmol/kg (n=136) of MultiHance. In Study B, patients with known metastatic disease to the CNS were randomized to receive two MRI evaluations with 0.05 mmol/kg (n=74) or 0.1 mmol/kg (n=76) of MultiHance. MRI scans were performed pre-contrast and within 5 minutes after each injection. The studies were designed to evaluate the effect of MultiHance MRI compared to the non-contrast MRI on a lesion level. Pre-contrast, post-contrast, and pre-plus-post contrast images (paired images) were independently evaluated by three blinded readers. The images were evaluated for the following endpoints using a scale from 0 to 4: the degree of lesion border delineation, the degree of visualization of lesion internal morphology, and the degree of lesion contrast enhancement. Lesion counting was also performed for the pre-contrast and paired image sets.

The 0.1 mmol/kg dose of MultiHance demonstrated consistently better visualization for all readers for all visualization endpoints. However, the 0.05 mmol/kg dose of MultiHance provided inconsistent visualization results between readers.

Comparison of pre-contrast versus post-contrast (0.1 mmol/kg) images showed that the mean score differences were significant and favored contrast for subjects in Study B (all subjects with known metastatic lesions) and for subjects with known tumors in Study A. However, the mean score differences between the pre-contrast and post-contrast images were not significant for non-tumor patients in Study A. These negative results may be attributed to a lack of lesion enhancement in non-tumor CNS disease.

Table 4 shows a comparison of paired images (pre-and post-contrast) versus pre-contrast images with respect to the difference in the mean score and with respect to the proportion of lesions read as better, worse, or the same as the pre-contrast MRI images. Table 4 shows that based on a lesion-level analysis 0.1 mmol/kg MultiHance provided a statistically significant improvement for the three structural parameters evaluated. Also, more lesions were seen in the paired images than in the pre-contrast images alone.

TABLE 4: LESION LEVEL RESULTS OF MRI CENTRAL NERVOUS SYSTEM ADULT STUDIES WITH 0.1 mmol/kg MULTIHANCE

	Study A			Study B		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
Endpoints	N = 395	N = 384	N = 299	N = 245	N = 275	N = 254
Border Delineation: Difference of Means [a]	0.8*	0.6*	0.8*	1.8*	1.5*	1.9*
Worse [b] Same Better	44 (11%) 146 (37%) 205 (52%)	61 (16%) 168 (44%) 155 (40%)	57 (19%) 89 (30%) 153 (51%)	13 (5%) 11 (5%) 221 (90%)	24 (9%) 19 (7%) 232 (84%)	15 (6%) 18 (7%) 221 (87%)
Internal Morphology: Difference of Means	0.8*	0.6*	0.7*	1.7*	1.4*	2.1*
Worse Same Better	37 (10%) 147 (37%) 211 (53%)	63 (17%) 151 (39%) 170 (44%)	62 (21%) 84 (28%) 153 (51%)	13 (5%) 16 (7%) 216 (88%)	26 (10%) 22 (8%) 227 (82%)	14 (5%) 22 (9%) 218 (86%)
Contrast Enhancement: Difference of Means	0.7*	0.5*	0.8*	1.9*	1.3*	1.9*
Worse Same Better	75 (19%) 148 (37%) 172 (44%)	74 (19%) 152 (40%) 158 (41%)	50 (17%) 109 (36%) 140 (47%)	13 (5%) 11 (5%) 221 (90%)	32 (12%) 21 (7%) 222 (81%)	17 (7%) 14 (5%) 223 (88%)

[a] Difference of means = (paired mean) – (pre mean)
[b] Worse = paired score is less than the pre score
Same = paired score is the same as the pre score
Better = paired score is greater than the pre score.
* Statistically significant for the mean (paired t test)

Pediatric 2 to 17 years

The efficacy and safety of MultiHance were evaluated in 92 pediatric patients with known or highly suspected disease of the central nervous system. MRI scans were performed pre-contrast and within 3 to 10 minutes following the administration of MultiHance 0.1 mmol/kg. Pre-contrast, post-contrast, and pre-plus-post contrast images (paired images) were independently evaluated by three blinded readers on a lesion level. The images were evaluated for the same endpoints as in the adult central nervous system trials using a scale from 0 to 4: the degree of lesion border delineation, the degree of visualization of lesion internal morphology, and the degree of lesion contrast enhancement. Lesion counting was also performed for the pre-contrast and paired image sets. The pre-contrast versus the paired image set was the primary comparison. Forty-nine percent of study subjects were male and the overall mean age was 10.6 years (range 2 to 17 years). The racial and ethnic representations were 77% Caucasian, 13% Asian, 5% Black, and 4% other racial or ethnic groups. MultiHance increased lesion border delineation, lesion internal morphology, and lesion contrast enhancement relative to non-contrast and these results were comparable to those seen in adults.

Pediatrics below 2 years

A study of 90 pediatric patients younger than 2 years of age was performed which supports extrapolation of CNS efficacy findings from adults and older pediatric patients. Three independent, blinded readers evaluated pre-contrast MRI image sets and paired pre-plus-post-contrast MRI image sets using MultiHance and rated the images according to three co-primary endpoints at a lesion level for the primary analysis. Two of the three readers reported improvement in the paired image sets in each of the three co-primary endpoints of lesion border delineation, visualization of lesion internal morphology, and lesion contrast enhancement.

14.2 MRA of Renal and Aorto-ilio-femoral Vessels

Safety and efficacy of MultiHance for use in MRA were evaluated in two prospective, multi-center, open-label, clinical trials (one for each arterial vascular territory: renal and aorto-ilio-femoral). Out of 580 patients who received MultiHance in these two trials, 62.2% were men and 90.9% were Caucasian; the average age was 63.4 years (range 18 to 93 years). In both trials, patients with known or suspected arterial disease underwent MRA with and without MultiHance as well as catheter-based digital subtraction angiography (DSA). Assessment of diagnostic efficacy for detecting/excluding clinically significant steno-occlusive disease (≥ 51% stenosis measured with electronic calipers) was based on comparisons of sensitivity and specificity between MultiHance MRA and non-contrast MRA, with DSA as a reference standard.

In each vascular territory, the primary efficacy analyses were designed to demonstrate superiority in sensitivity and non-inferiority in specificity of MultiHance MRA to non-contrast MRA at the vessel-segment level. The interpretation of MRA images from both trials was conducted by three independent radiologist readers who were blinded to clinical data, including the DSA results. The pre-specified success criteria were to be achieved by at least the same two readers for all primary analyses.

Results of both trials showed a statistically significant increase in sensitivity and specificity of MultiHance MRA over non-contrast MRA in detecting clinically significant steno-occlusive disease. Table 5 summarizes the efficacy results by reader.

Table 5: PERFORMANCE CHARACTERISTICS OF MULTIHANCE-MRA AND NON-CONTRAST MRA

READER	SENSITIVITY			SPECIFICITY		
	AORTO-ILIO-FEMORAL ARTERIES					
	MultiHance MRA [A]	Non-contrast MRA [B]	[A] – [B] (95% CI)	MultiHance MRA [A]	Non-contrast MRA [B]	[A] – [B] (95% CI)
1	77.8%	73.7%	4.5 (1.5, 7.6)	88.1%	78.5%	10.0 (7.3, 12.6)
2	65.2%	52.5%	12.6 (8.5, 16.6)	94.2%	89.4%	4.9 (2.7, 7.1)
3	69.0%	59.1%	10.0 (6.1, 14.0)	90.0%	75.3%	14.9 (12.1, 17.8)
	RENAL ARTERIES					
	SENSITIVITY			SPECIFICITY		
	MultiHance MRA [A]	Non-contrast MRA [B]	[A] – [B] (95% CI)	MultiHance MRA [A]	Non-contrast MRA [B]	[A] – [B] (95% CI)
1	67.8%	47.0%	20.8 (12.8, 28.9)	94.0%	86.1%	8.3 (4.2, 12.4)
2	62.4%	46.7%	16.2 (6.8, 25.6)	94.0%	83.5%	10.3 (5.5, 15.0)
3	65.5%	39.6%	25.3 (15.9, 34.6)	94.7%	87.3%	8.0 (3.6, 12.5)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MultiHance (gadobenate dimeglumine) is a clear, colorless to slightly yellow solution containing 529 mg gadobenate dimeglumine per mL. MultiHance is supplied in glass vials; each single dose vial is rubber stoppered with an aluminum seal and the contents are sterile. MultiHance is supplied in boxes of:

Five 5 mL single dose 10 mL vials (NDC 0270-5164-12)
Five 10 mL single dose 20 mL vials (NDC 0270-5164-13)
Five 15 mL single dose 20 mL vials (NDC 0270-5164-14)
Five 20 mL single dose 20 mL vials (NDC 0270-5164-15)

16.2 Storage and Handling

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Do not freeze.

17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Nephrogenic Systemic Fibrosis

Instruct patients to inform their physician if they:
- have a history of kidney and/or liver disease, or
- have recently received a GBCA.

GBCAs increase the risk for NSF among patients with impaired elimination of the drugs. To counsel patients at risk for NSF:
- Describe the clinical manifestations of NSF
- Describe procedures to screen for the detection of renal impairment.

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following MultiHance administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

Common Adverse Reactions

Inform patients that they may experience:
- reactions along the venous injection site, such as mild and transient burning or pain or feeling of warmth or coldness at the injection site
- side effects of feeling hot, nausea, and headache.

Gadolinium Retention

Advise patients that gadolinium is retained for months or years in brain, bone, skin, and other organs in patients with normal renal function. The clinical consequences of retention are unknown.

Retention depends on multiple factors and is greater following administration of linear GBCAs than following administration of macrocyclic GBCAs [see ***Warnings and Precautions (5.3)***].

Rx only

US Patent No. 4,916,246

Manufactured for

Bracco Diagnostics Inc. - Monroe Township, NJ 08831

By BIPSO GmbH - 78224 Singen (Germany)

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MEDICATION GUIDE
MULTIHANCE® (*məl-tē-han(t)s*)
(gadobenate dimeglumine)
Injection for intravenous use

What is MULTIHANCE?

- MULTIHANCE is a prescription medicine called a gadolinium-based contrast agent (GBCA). MULTIHANCE, like other GBCAs, is injected into your vein and used with a magnetic resonance imaging (MRI) scanner.
- An MRI exam with a GBCA, including MULTIHANCE, helps your doctor to see problems better than an MRI exam without a GBCA.
- Your doctor has reviewed your medical records and has determined that you would benefit from using a GBCA with your MRI exam.

What is the most important information I should know about MULTIHANCE?

- MULTIHANCE contains a metal called gadolinium. Small amounts of gadolinium can stay in your body including the brain, bones, skin and other parts of your body for a long time (several months to years).
- It is not known how gadolinium may affect you, but so far, studies have not found harmful effects in patients with normal kidneys.
- Rarely, patients have reported pains, tiredness, and skin, muscle or bone ailments for a long time, but these symptoms have not been directly linked to gadolinium.
- There are different GBCAs that can be used for your MRI exam. The amount of gadolinium that stays in the body is different for different gadolinium medicines. Gadolinium stays in the body more after Omniscan or Optimark than after Eovist, Magnevist, or MultiHance. Gadolinium stays in the body the least after Dotarem, Gadavist, or ProHance.
- People who get many doses of gadolinium medicines, women who are pregnant and young children may be at increased risk from gadolinium staying in the body.
- Some people with kidney problems who get gadolinium medicines can develop a condition with severe thickening of the skin, muscles and other organs in the body (nephrogenic systemic fibrosis). Your healthcare provider should screen you to see how well your kidneys are working before you receive MULTIHANCE.

Do not receive MULTIHANCE if you have had a severe allergic reaction to GBCAs including gadobenate dimeglumine, or any of the ingredients in MULTIHANCE.

Before receiving MULTIHANCE, tell your healthcare provider about all your medical conditions, including if you:

- have had any MRI procedures in the past where you received a GBCA. Your healthcare provider may ask you for more information including the dates of these MRI procedures.
- are pregnant or plan to become pregnant. It is not known if MULTIHANCE can harm your unborn baby. Talk to your healthcare provider about the possible risks to an unborn baby if a GBCA such as MULTIHANCE is received during pregnancy
- have kidney problems, diabetes, or high blood pressure.
- have had an allergic reaction to dyes (contrast agents) including GBCAs

What are the possible side effects of MULTIHANCE?

- **See "What is the most important information I should know about MULTIHANCE?"**
- **Allergic reactions. MULTIHANCE can cause allergic reactions that can sometimes be serious. Your healthcare provider will monitor you closely for symptoms of an allergic reaction.**

The most common side effects of MULTIHANCE include: nausea, headache, feeling hot, or burning at the injection site.

These are not all the possible side effects of MULTIHANCE.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of MULTIHANCE.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider for information about MULTIHANCE that is written for health professionals.

What are the ingredients in MULTIHANCE?

Active ingredient: gadobenate dimeglumine

Inactive ingredients: water

Manufactured by: BIPSO GmbH-78224 Singen (Germany)

Manufactured for: Bracco Diagnostics Inc., Monroe Township, NJ 08831

US Patent No. 4,916,246

For more information, go to www.imaging.bracco.com or call 1-800-257-5181.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 04/2018

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