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Selection of a Macrocyclic GBCA: Barrow Neurological Institute's Experience

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By Cindy Schultz, PhD

John Karis, MD, is the Director of MRI and Brain Imaging in the Department of Neuroradiology at Barrow Neurological Institute, part of Dignity Health St. Joseph's Hospital and Medical Center, in Phoenix, AZ. In 2017, Dr. Karis and his team were tasked with selecting a macrocyclic gadolinium-based magnetic resonance imaging (MRI) contrast agent. Here we describe how the team went about making the selection, and their subsequent experience with that agent, ProHance (gadoteridol), since they made the switch.

"When we first decided to try ProHance in the outpatient imaging area, I did talk to the techs ahead of time and told them that if the switch wasn't the right thing to do clinically, we wouldn't do it."

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Background

The first gadolinium-based contrast agent (GBCA) approved for use by the U.S. Food and Drug Administration (FDA) was the linear agent Magnevist (gadopentetate dimeglumine) in 1988, followed by the macrocyclic agent ProHance in 1992. Both Magnevist and ProHance are non–tissue-specific, extracellular fluid (ECF), multi-use agents that were initially approved for imaging the central nervous system (CNS). Since then, several additional GBCAs have been approved, and there are now 6 multi-use agents approved for use in the United States for a variety of indications.

Several factors differentiate the 6 contrast agents approved for MRI of the CNS.[1-9] (Table 1) In terms of physicochemical properties, they vary in chemical structure (macrocyclic vs linear), ionicity (ionic vs. non-ionic), and gadolinium concentration (0.5M vs 1.0M). In addition, all possess similar T1-relaxivity, with the exception of MultiHance (gadobenate dimeglumine), a high-relaxivity GBCA. ProHance, the macrocyclic agent that has been on the market longest in the U.S. is also the only agent approved at up to triple the standard 0.1 mmol/kg dose.

Stability, the strength with which the GBCA chelate holds on to the gadolinium ion, is another differentiator of the GBCAs: those with a macrocyclic chelate bind most tightly to the gadolinium and thus are characterized as high-stability. MultiHance, the high-relaxivity linear agent, is considered intermediate-stability, while the conventional-relaxivity, linear agents have the lowest stability, with the greatest propensity to release gadolinium, albeit in trace amounts with no indication of clinical consequences.[7,9] (Table 1) In 2006, it was reported that the use of the linear GBCAs Magnevist, Omniscan, and OptiMARK (no longer available in the U.S.) was associated with the potential for development of nephrogenic systemic fibrosis (NSF) in patients with severe renal dysfunction. Although the pathogenesis of NSF is still unknown,

Table 1. Currently Available GBCAs Approved for MRI of the CNS[1-9]

Trade Name	Generic Name	Chemical Structure	Concentration (M)	Stability	Approved dose (mmol/kg)*	ACR Group**
ProHance	Gadoteridol	Macrocyclic	0.5	High	0.1 + 2nd dose of 0.2 up to 30 min after 1st dose if needed (A); 0.1 (P)	II
Gadavist	Gadobutrol	Macrocyclic	1.0	High	0.1	II
Dotarem	Gadoterate meglumine	Macrocyclic	0.5	High	0.1	II
MultiHance	Gadobenate dimeglumine	Linear	0.5	Medium	0.1	II
Magnevist	Gadopentetate dimeglumine	Linear	0.5	Low	0.1	I
Omniscan	Gadodiamide	Linear	0.5	Low	0.1	I

*A=adult; P=pediatric.
**Group I=Agents associated with the greatest number of NSF cases; Group II=Agents associated with few, if any, unconfounded cases of NSF.

at that time stability became a very important property of GBCAs, because the vast majority of unconfounded cases of NSF were associated to GBCAs with the lowest stability, especially linear nonionic.[10] As a result, the American College of Radiology (ACR) stratified the GBCAs based on NSF risk: the macrocyclic agents and the high-relaxivity linear agent MultiHance were grouped together, and the risk of NSF with these Group II agents was considered to be "sufficiently low or possibly nonexistent," such that patients did not require renal function screening prior to administration.[9] (Table 1) To date, the vast majority of NSF cases have been shown to occur following administration of a low-stability, linear GBCA, and few unconfounded (single-agent) cases of NSF have been described following use of a macrocyclic agent. Among the macrocyclic agents, Gadavist has been associated with three unconfounded cases of NSF.[11]

More recently, a number of published findings showed gadolinium retention in the brains of patients who had received contrast in the past.[12] Although such reports showed that gadolinium retention can be seen following administration of any of the GBCAs, all preclinical studies indicate greater levels of gadolinium retention with the linear agents than with the macrocyclic ones.[13] Even among the macrocyclic agents, there seem to be differences in gadolinium retention: studies show ProHance is associated with less gadolinium retention in bone and brain compared to Gadavist.[14,15] More significant for healthcare professionals, in patients with normal renal function, no harmful or adverse clinical effects have been associated with gadolinium retention in the brain or body.[15] While the FDA has required the addition of precautionary statements regarding gadolinium retention in the GBCA product labels, importantly the FDA also noted that the clinical consequences of gadolinium retention have not been established in patients with normal renal function.[16] Nevertheless, both NSF and gadolinium retention have prompted institutions that offer radiologic services to reevaluate the GBCAs they routinely offer as part of their clinical practice.

"With respect to safety, we were very happy with ProHance. Another thing I like about ProHance is that it's the usual concentration. With Gadavist, the techs have to do calculations and adjust to half the volume, which can be challenging."

Peggy Islas, BS RT(R)(MR) MRSO(MRSC)
MRI Safety Officer
Lead Technologist, MRI
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Barrow Neurological Institute

Barrow Neurological Institute, established in 1961, is a large, world-class neuroscience center with 8 clinical MRI scanners, including an intraoperative scanner, and an MRI research facility. The volume of MRI scanning at Barrow Neurological Institute is impressive,

Table 2. Adverse Event Rates with Currently Available ECF GBCAs[1-6]

Contrast Agent	Generic Name	No. of Patients	Headache (%)	Nausea (%)	Taste Perversion (%)	Rash (%)
ProHance	Gadoteridol	1,251	<1.0	1.4	1.4	<1.0
Gadavist	Gadobutrol	6,809	1.5	1.1	0.4	0.3
Dotarem	Gadoterate meglumine	2,813	0.5	0.6	<0.2	<0.2
MultiHance	Gadobenate dimeglumine	4,967	1.2	1.3	0.7	<0.5
Magnevist	Gadopentetate dimeglumine	1,272	4.8	2.7	<1.0	<1.0
Omniscan	Gadodiamide	1,160	≤3.0	≤3.0	≤1.0	≤1.0

ECF=extracellular fluid; GBCA=gadolinium-based contrast agent.

with approximately 95 MRI exams per day, and over 31,000 MRI exams per year. The MRI scanners at Barrow Neurological Institute are used to perform inpatient, outpatient, and emergency department (ED) diagnostic exams, with a minimum of two scanners running on a 24/7 basis. In addition, the magnets are used for surgical planning and intraoperative MRI, as well as for pulse sequence research and development.

Dr. Karis arrived at Barrow Neurological Institute in the early 1990s, soon after GBCAs were approved for use. Early on, Magnevist was used, followed by a switch to Omniscan (gadodiamide). In the late 1990s, due to a combination of early reports of NSF, as well as the higher relaxivity, Dr. Karis' group switched to MultiHance, and continued to use MultiHance for a number of years. However, starting in 2014, several groups reported T1-weighted signal hyperintensity in the brains of patients on noncontrast scans (reviewed in McDonald, 2018), indicating gadolinium retention.[12] As mentioned above, these signal hyperintensities could be found in patients that had received any GBCA, but appeared to be less pronounced with the macrocyclic GBCAs. As a result of these findings, as well as public concern around gadolinium retention, in January of 2017, Dr. Karis and colleagues decided to switch again, this time to a macrocyclic agent.

"Before we switched to ProHance, we did an internal research project, noting any difference in adverse reactions – they all get reported out anyway – and it's just not there."

Richard Sherry, MHA, MPH, RT(R)(MR)
Manager of Radiology Services, MRI
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Switching to a Macrocyclic GBCA

Dr. Karis had had some prior experience with Gadavist at another institution, so this was the macrocyclic initially selected; however, after a brief period, due largely to positive experience with Bracco contrast agents in X-ray and computed tomography (CT), and the potential advantages of standardizing system-wide with Bracco products, Dr. Karis decided to evaluate ProHance. Based on relaxivity, Dr. Karis trusted that the image quality would be there, so his focus was on patient tolerability. Specifically, before the switch could be made, it was necessary to ensure that in terms of patient safety, there would be no disadvantages. Dr. Karis approached the decision cautiously, deciding to administer ProHance to 100 patients in the outpatient imaging department to evaluate whether there was any increase in adverse events (AEs), specifically nausea and vomiting. Based on the Prescribing Information (PI),

Dr. Karis knew that there were no reported differences in AE rates among the macrocyclic agents (Table 2), so he did not anticipate an increase. However, he wanted the technologists to feel comfortable knowing that the patients' safety and comfort was paramount, and that their final selection of GBCA would be based on what was best for the patient.

Barrow Neurological Institute's Experience with ProHance

Once the 100-patient ProHance study was complete, it was apparent that there was no increase in any AEs. At that point, Dr. Karis instructed that ProHance be rolled out facility-wide, and ProHance use was expanded to include inpatients and ED patients. ED patients often receive ProHance injection as a bolus, where one might anticipate an increased incidence of nausea, but no increase was seen. Dr. Karis reported that they now use ProHance routinely, keeping other agents on formulary only in the event that if a patient has an allergic-type reaction to one agent, they can then administer a different agent.

Considerations in Switching to ProHance

The facility's MRI technologists required no special training prior to the switch. Dr. Karis shared the PI data with the technologists so they would know there was no scientific basis upon which to anticipate an increase in AEs with ProHance. Ultimately, the MRI technologists concurred that they did not see any change in the AE rate with ProHance in any of the imaging settings. By the end of 2017, Barrow Neurological Institute reported that they use ProHance almost exclusively (>95%) for all of their MRI examinations.

Barrow now uses Bracco contrast media and delivery products institution-wide for X-ray, CT, and MRI. As a result of this standardization, Dr. Karis' group has the added benefit of considerable cost savings, which they can use elsewhere in the imaging department to upgrade equipment, bring on staff, or make other improvements.

"From the technologist's perspective, our big concern was contrast reactions, specifically nausea and vomiting. During our evaluation of ProHance, we did not see any more contrast reactions with ProHance versus Gadavist."

Mark Mahl, RT(R)(MR)
Lead Technologist, MRI
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CASE STUDY

MRI of 76-year-old male with slurred speech, confusion, and psycho-motor retardation

Case Summary

A 76-year-old man presents to the Emergency Department with a 3-week history of slurred speech, confusion, and psychomotor retardation that has progressed more rapidly over the past 3 days. The patient has a remote history (21 years ago) of non-Hodgkin's lymphoma. MRI of the head was performed on a 1.5T GE scanner. The patient received 16 mL of ProHance IV without complication. Precontrast axial T1-weighted and FLAIR images, as well as postcontrast axial and coronal T1-weighted images, are shown in Figure 1.

Imaging Findings

Several patchy areas of subcortical FLAIR signal hyperintensity with associated contrast enhancement are present in the cerebral hemispheres bilaterally. There is no associated hemorrhage or cystic necrosis and relatively little adjacent white matter edema or mass effect.

Diagnosis

B-Cell Lymphoma

Conclusion

Differential considerations include lymphoma, an acute demyelinating process such as acute disseminated encephalomyelitis (ADEM), gliomatosis cerebri, and parenchymal sarcoid. CNS lymphoma was confirmed by biopsy. CNS lymphoma in immunocompetent subjects characteristically occurs in males in their 6th or 7th decade of life. The effectiveness of treatment, which includes a combination of radiation and chemotherapy, is improved in immunologically normal patients.

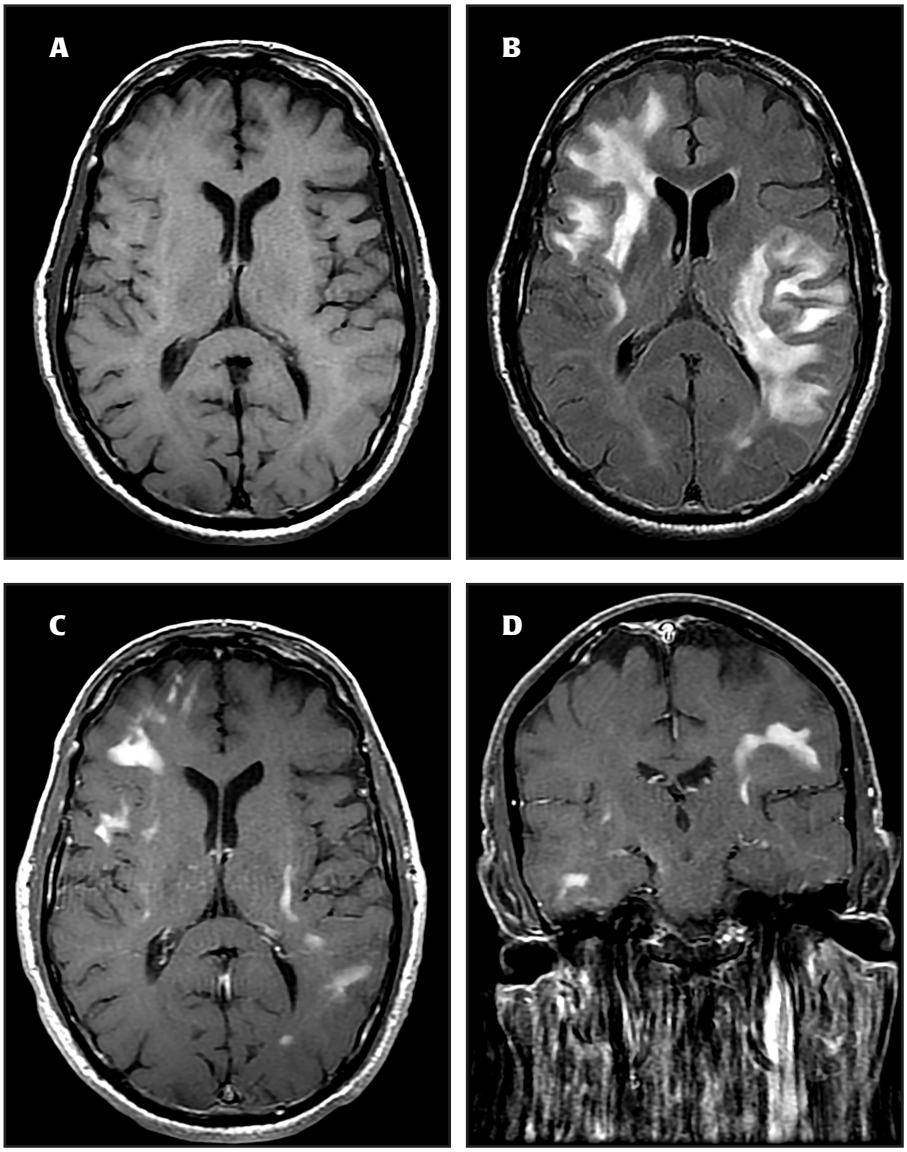

FIGURE 1. *Precontrast axial T1-weighted (A) and FLAIR (B) images, and postcontrast axial (C) and coronal (D) T1-weighted images of the head.*

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Bracco Diagnostics

Rx ONLY
Please see full prescribing information. A brief summary follows.

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.

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 hepatobiliary 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 orallergic 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/m2 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/m2 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: 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 preexisting cardiovascular disorders. **Digestive:** Increased Salivation; Dysphagia Nervous System: Stupor; Tremor; Loss of Consciousness Respiratory System: 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.

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.

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LIFE FROM INSIDE