PRODUCT MONOGRAPH

ProHance®

(Gadoteridol) injection
279.3 mg (0.5mmol) per mL

CONTRAST ENHANCEMENT PREPARATION

FOR

MAGNETIC RESONANCE IMAGING (MRI)

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Date of Revision: 09 March 2018

Control No.: 212409

ProHance®

(gadoteridol) injection
279.3 mg (0.5mmol) per mL
for Intravenous Use

Therapeutic classification

Contrast Enhancement Preparation for Magnetic Resonance Imaging (MRI)

Actions and clinical pharmacology

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.

The current evidence suggests that gadolinium may accumulate in the brain after repeated administrations of GBCAs although the exact mechanism of gadolinium passage into the brain has not been established.However, 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 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.

Eighty percent of the drug is cleared from the body of patients with normal renal function within 6 hours of administration and is exclusively eliminated in the urine with 94.4±4.8% (mean±SD) of the dose excreted within 24 hours post-injection. There is no detectable biotransformation or decomposition of gadoteridol.

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.

Gadoteridol does not bind to rat serum protein *in vitro*. There was no evidence *in vivo* of

free gadolinium release in mice.

Indications and clinical use

ProHance ® (gadoteridol) injection is indicated in adults and children 2 years of age and older for contrast enhancement of magnetic resonance imaging (MRI) of brain, spine and surrounding tissues in conditions with expected vascular abnormality or defective blood-brain barrier. Due to limited clinical trial experience, ProHance ®is not recommended for use for children less than two years of age.

Use of macrocyclic agents may be preferable in potentially vulnerable patients such as children.

ProHance ® (gadoteridol) injection is also indicated in adults for contrast enhancement of MRI of extracranial and extraspinal head and neck pathology.

Contraindications

Hypersensitivity to ProHance ® (gadoteridol) injection or its components.

Warnings

ProHance ® (gadoteridol) injection should be administered only by a radiologist experienced in magnetic resonance imaging (MRI) procedures.

As with other contrast materials, hypersensitivity reactions may rarely occur. Adequate equipment and drugs for the treatment of a possible anaphylactic reaction should be readily available.

Patients with history of allergy or drug reactions should be observed for several hours after drug administration.

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 ®injection 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.

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS
Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with:

- chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/I.73m2) or
- acute renal failure / acute kidney injury.

In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a GBCA, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration. (See Nephrogenic Systemic Fibrosis, Skin, Renal, and Post-Market sections)

Convulsive states
In controlled clinical trials with ProHance ®, no seizure activity in patients with a history of grand mal seizure was observed. However, as this phenomenon has been reported with other contrast media, caution should be exercised in patients with this clinical history.

Nephrogenic Systemic Fibrosis (NSF)
Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/l. 73m2), or acute renal failure / acute kidney injury. In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). For patients receiving hemodialysis healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if hemodialysis prevents NSF.

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 function impairment at the time of exposure.

NSF development is considered a potential class-related effect of all GBCAs.

Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan®), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®). The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA.

The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephro1 2006; 17:2359). The risk, if any for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a GBCA, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration. (See Pharmacology and Dosage and Administration).

A skin biopsy is necessary in order to exclude the diagnosis of similarly presenting skin disorders (e.g scleromyxedema). (See Warnings, Renal, Skin and Post-Market sections).

Renal
Exposure to GBCAs increases the risk for NSF in patients with:

- chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/l.73m2), or
- acute renal failure / acute kidney injury.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. The risk, if any for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable. (See Warnings, Nephrogenic Systemic Fibrosis, Skin, and Post-Marketing sections).

Skin

NSF was first identified in 1997 and has so far, been observed only in patients with renal disease. This is a systemic disorder with the most prominent and visible effects on the skin. Cutaneous lesions associated with this disorder are caused by excessive fibrosis and are usually symmetrically distributed on the limbs and trunk. Involved skin becomes thickened which may inhibit flexion and extension of joints and result in severe contractures. The fibrosis associated with NSF can extend beyond dermis and involve subcutaneous tissues, striated muscles, diaphragm, pleura, pericardium, and myocardium. NSF may be fatal. (See Warnings, Nephrogenic Systemic Fibrosis, Renal, and Post-Market sections).

Use in Pregnancy

There are no adequate and well-controlled studies in pregnant women. ProHance™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated GBCA doses may need to be considered due to individual clinical circumstances and in other potentially vulnerable patients such as pregnant women.

Nursing Mothers

It is not known to what extent ProHance ®is excreted in human milk. If ProHance ®is given to nursing mothers, breast-feeding should be discontinued for 24 hours following its administration.

Accumulation of Gadolinium in Brain

The current evidence suggests that gadolinium may accumulate in the brain after multiple administrations of GBCAs. Increased signal intensity on non-contrast T1-weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus. The evidence suggests that the risk of gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents.

The clinical significance of gadolinium accumulation in the brain is presently unknown; however, gadolinium accumulation may potentially interfere with the interpretation of MRI scans of the brain. In order to minimize potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

Precautions

Use in Renally Impaired Patients

Since gadoteridol is cleared from the body by glomerular filtration, caution should be exercised in patients with severely impaired renal function. A suitable interval of time, greater than 24 hours (preferably 48 hours), should elapse between 2 separate examinations with ProHance ®or between evaluations with iodine contrast media and ProHance™. ProHance ®injection has been shown to be dialyzable in *in vitro* experiments. (See Warnings, Nephrogenic Systemic Fibrosis, Renal)

Geriatric Patients

No specific precautions other than those pertinent to MRI and ProHance ®in general are applicable for elderly patients.

Pediatric Patients

The cautious utilization of the lowest possible dose of ProHance ®is recommended in the pediatric population. Due to limited clinical trial experience, ProHance ®is not recommended for use for children less than two years of age. (See Dosage and Administration, and Warnings, Nephrogenic Systemic Fibrosis, Renal).

Use of macrocyclic agents may be preferable in potentially vulnerable patients such as children.

Hypersensitivity Reactions

The possibility of a reaction, including serious life threatening, fatal anaphylaxis, or other idiosyncratic reactions, should always be considered, especially in patients with a history of known clinical hypersensitivity.

Adverse Reactions

The most commonly noted adverse events are taste perversion and nausea with an incidence of 1.43% each. These events were mild to moderate in severity.
The following adverse events were reported in clinical trials (1184 patients) with ProHance ® (gadoteridol) injection at doses of 0.05 to 0.3 mmol/kg. All adverse events are included regardless of causal relationship to ProHance ®administration.

Adverse Event	**Incidence by Event (%)**
Body as a whole	
Abdominal cramps	0.08
Erythema at I.V. site	0.08
Fever	0.08
Flushed feeling	0.17
Neck rigid	0.08
Pain chest	0.08
Pain injection site	0.34
Cardiovascular System	
A-V nodal rhythm	0.08
Elevated heart rate	0.08
Hypotension	0.34
Prolonged P-R interval	0.08
Digestive System	
Dry mouth	0.25
Gingivitis	0.17
Loose bowel	0.08
Nausea	1.43
Vomiting	0.34
Nervous System	
Anxiety	0.17
Dizziness	0.25

Headache	0.68
Paresthesia	0.42
Staring episode	0.08
Syncope	0.08
Respiratory System	
Cough	0.08
Dyspnea	0.08
Allergic/Pseudoallergic	
Edema face	0.08
Edema tongue	0.08
Hive	0.25
Itching tongue	0.08
Itching watery eyes	0.17
Pruritus	0.25
Rash	0.17
Rash maculopapular	0.08
Rhinitis	0.17
Tingling sensation in extremity and digits	0.08
Tingling sensation in throat	0.08
Urticaria	0.17
Special senses	
Taste perversion	1.43
Tinnitus	0.08

The following adverse drug reactions have also been reported:

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, seizure

Respiratory: Apnea, wheezing

Skin and Appendages: Sweating and cyanosis

Special Senses: Voice alteration, transitory deafness

Urogenital: Urinary incontinence

Post-Market Adverse Drug Reactions

Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan®), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance ®).

The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA. The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006; 17:2359). The risk, if any for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable.

(See Warnings, Nephrogenic Systemic Fibrosis, Skin, and Renal sections)

Symptoms and treatment of overdosage

There has not been any case of overdose reported to date; consequently neither the signs nor the symptoms of overdosage have been identified. In clinical studies using doses up to 0.3 mmol/kg, no clinical consequences related to increasing dose have been observed.

Should an overdose occur, the patient should be carefully observed and given symptomatic and supportive treatment.

The LD_{50} of intravenously administered ProHance ® (gadoteridol) injection is greater than 10 mmol/kg in mice and rats.

Dosage and Administration

ProHance ® (gadoteridol) injection should be inspected visually for particulate matter and discoloration prior to administration. If either is present, the vial should be discarded. ProHance ®is supplied in single dose vials. Unused portions of solution should be discarded. The product should not be frozen.

The lowest effective dose should be used.

Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated GBCA doses may need to be considered due to individual clinical circumstances and in other potentially vulnerable patients such as children and pregnant women **(See Warnings and Precautions).**

CENTRAL NERVOUS SYSTEM

The recommended dosage of ProHance ®is 0.1 mmol/kg (0.2 mL/kg), administered as a rapid intravenous infusion (up to 1 mL/sec) or as a bolus. Doses up to 0.3 mmol/kg have been safely administered during clinical trials.

The cautious utilization of the lowest possible dose of ProHance ®is recommended in the pediatric population. Due to limited clinical experience, ProHance ®is not recommended for use for children less than two years of age.

EXTRACRANIAL/EXTRASPINAL TISSUES

The recommended dosage of ProHance ®is 0.1 mmol/kg (0.2 mL/kg), administered as a rapid intravenous infusion (up to 1 mL/sec) or as a bolus.

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 injection of ProHance ®.

If in the clinical judgment of the physician, sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body. In clinical trials with ProHance ®, repeat injections have been safely administered within 30 minutes of an initial injection. Since pharmacokinetic studies have not been carried out in patients with renal impairment, they should be closely monitored. ProHance ®has been shown to be dialyzable in *in vitro* experiments.

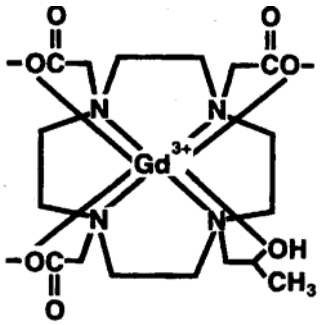
Pharmaceutical Information

DRUG SUBSTANCE

Proper name: Gadoteridol (USAN)

Chemical name: 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tri-acetic acid, gadolinium complex.

Structural formula:



Molecular formula: $C_{17}H_{29}N_4O_7Gd$

Molecular weight: 558.7

Description: Gadoteridol is a white to off white crystalline powder freely soluble in water or methanol and soluble in isopropanol. A 10.1 mg/mL aqueous solution has a pH of 6.5.

COMPOSITION

ProHance ® (gadoteridol) injection is a clear, colorless to slightly yellow sterile aqueous solution. Each mL contains 279.3 mg (0.5 mmol) of gadoteridol with 0.23 mg (0.00025 mmol) calteridol calcium and 1.21 mg (0.01 mmol) of tromethamine. The pH is adjusted to 6.5 to 8.0 with hydrochloric acid and/or sodium hydroxide. Contains no preservatives.

ProHance ®has an osmolality approximately twice that of plasma (630 mOsmol/kg water at 37°C) and is hypertonic under conditions of use. It has a density of 1.138 g/mL at 20°C and a viscosity of 2.0 cP at 20°C and 1.3 cP at 37°C.

STORAGE RECOMMENDATIONS
ProHance ®should be stored at controlled room temperature (15 to 30°C) and protect from light.

ProHance ®is supplied in single dose vials. Unused portions of solutions should be discarded.

Availability of dosage forms

ProHance ® (gadoteridol) injection 279.3 mg (0.5 mmol)/mL is available in 10, 15 and 20 mL single dose vials, 50 mL Pharmacy Bulk Package, 10 mL and 17 mL single dose syringes.

Directions for Proper Use of Pharmacy Bulk Package

a. The transfer of ProHance ®from the Pharmacy Bulk Package should be performed in a suitable work area, such as a laminar flow hood, using aseptic technique.
b. The container closure may be penetrated only one time, utilizing a suitable transfer device.
c. The withdrawal of container contents should be accomplished without delay. A maximum time of 8 hours from initial closure entry is permitted to complete fluid transfer.
d. Storage temperature of container after the closure has been entered should not exceed 25˚C.

PHARMACOLOGY

PHARMACOKINETICS

Tissue Distribution in Mice

The tissue distribution of gadoteridol was studied following intravenous administration of 0.1 mL of the ^{153}Gd-labeled chelate to unanesthetized male mice (approximately 0.24 mmol/kg).
Groups of five mice were injected and sacrificed at times ranging from 5 minutes to 14 days after injection.

The blood clearance of gadoteridol was rapid and complete with only 0.6% of the injected dose remaining in the blood pool at one hour after injection. The amount excreted into the urine at one hour was 88.2 ± 5.4%.

The tissue distribution profile reflected the rapid clearance from the blood with relatively high uptake in all tissues evaluated with the exception of brain. All tissue levels decreased rapidly over the first 60 minutes post injection as the activity in the urinary bladder rose to 88% of the injected dose. Tissue levels at 24 hours post injection were at a very low level (a total of 1.33 ± 0.19% of injected dose remaining) and continued to decline further over the 14 days of observation.

There was no evidence *in vivo* of release of free gadolinium.

Pharmacokinetics in Man

Groups of 3 normal subjects received single intravenous doses of 0.05, 0.10, 0.15, 0.25 or 0.30 mmol/kg of gadoteridol as ProHance® (gadoteridol) injection. Blood samples were drawn at
1, 2, 3, 4, 5, 10, 15, 30, 60, 120, and 240 minutes post-dose as well as after 24 hours. Cumulative urine samples were obtained at 1 minute, 1 hour, 4 hours and 24 hours after injection.

The results obtained conform to a two-compartment open model with a mean distribution half-life of 0.20 ± 0.04 hour and a mean elimination half-life of 1.57 ± 0.08 hours. Over 94% (94.4 ± 4.8%) of the injected dose was excreted in the urine within 24 hours. Renal and plasma clearance rates were virtually identical (1.41 ± 0.33 mL/min/kg and 1.50 ± 1.35 mL/min/kg, respectively).

SPECIAL STUDIES

CNS Effects in Mice and Rats

The effect of single intravenous doses of 0.5, 1.5 and 5.0 mmol/kg gadoteridol (as the ProHance® formulation) was assessed in the following models:

Method	Species	# per group	Fasting
Hexobarbital Sleeping Time	Mouse	10	overnight
HBE Test [1]	Mouse	10	overnight
Traction Test	Mouse	10	overnight
Catalepsy	Rat	10	overnight
Catalepsy	Mouse	10	overnight
Pentetrazole Seizures	Mouse	10	overnight
Orientation Motility	Mouse	10	about 3 hours
Spontaneous Motility	Mouse	10	about 6 hours
Reflexes[2]	Rat	5 x 1	not fasted

1 Hot plate, Balance Rod, Electroshock
2 Linguomandibular reflex and tibial nerve transmission

At a dose of 5.0 mmol/kg, the gadoteridol formulation markedly inhibited orientation motility in mice. No such effect was seen at the lower doses. Gadoteridol had neither muscle-relaxant, analgetic, anticonvulsive, nor cataleptic properties. Administration did not affect central coordination in mice, did not stimulate spontaneous motility in mice and did not potentiate hexobarbital anesthesia in mice. The linguomandibular reflex and neuromuscular transmission in rats were not inhibited.

Effects on Sensory, Neuromuscular and Reflexive Functions in Rats

The ProHance® formulation was administered intravenously to three groups of 4 male and 4 female Harlan Sprague Dawley rats at gadoteridol single doses of 0.5, 1.5 and 5 mmol/kg. An additional group given 0.9% saline at 10 mL served as control. A battery of tests to evaluate sensory, neuromuscular and reflexive functions was conducted before dosing, immediately after dosing and 4 hours after dosing. These tests included the Preyer reflex, pinnal reflex, corneal reflex, visual placing, tail and toe pinch reflex, back righting reflex, hooded free-fall righting reflex, and forelimb grip strength.

There were no significant differences in any of these tests at any testing time between treated and control rats.

Cardiovascular and Renal Safety in Dogs

The ProHance® formulation was administered intravenously to 3 anesthetized beagle dogs (2♂, 1♀) at 0.1, 0.25, 0.6 and 1.5 mmol/kg, with 1 hour between doses. Heart and respiratory rates, electrocardiograms, cardiac output, blood pressure, left ventricular blood pressure, renal blood flow, glomerular filtration rate, blood gases and pH, and serum and urinary electrolyte concentrations were measured for one hour prior to the first dose and for one hour after each dose.

At doses of 0.1 to 1.5 mmol/kg ProHance® caused slight increases in urinary sodium (~ 20-150%) and potassium (~10-65%) excretions. In addition, slight decreases in blood pressure
(~10-20%) and left ventricular systolic pressure (~10-20%) were observed after administration of 0.1 mmol/kg, but these lasted only three minutes or less. Moderate decreases in blood pressure (~ 25-55%) and left-ventricular systolic pressure (~ 20-30%) were seen for 15 minutes to 1 hour postdose following injections of 0.25 to 1.5 mmol/kg.

Also observed at doses of 0.25 to 1.5 mmol/kg were slight decreases in serum sodium (1-2%); slight to moderate decreases in dP/dT (maximum); slight increases in renal blood flow (up to 30%), respiratory rate (up to 3 fold), and PQ intervals; and slight to moderate increases in dP/dT (minimum). After 0.6 to 1.5 mmol/kg, slight increases in urine pH and left-ventricular end-diastolic pressure (~50-150%), as well as a slight decrease in time to dP/dT (maximum) were noted. Additional changes seen after doses of 1.5 mmol/kg included a slight transient decrease in serum protein (~10-20%), a slight to moderate decrease in heart rate (~ 20-50%), and slight increases in urine output (~10-35%), glomerular filtration rate (~5-10%), stroke volume (~20-50%), and QT and QRS intervals.

Hemostatis in Dogs
The ProHance® formulation was administered as a single intravenous gadoteridol dose of 1.5 mmol/kg to two male and two female dogs. Injections were given at a rate of about 0.5 mL/sec.

Bleeding time, blood clotting time, plasma prothrombin time, activated partial thromboplastin time and serum iron were determined prior to the dose of 5, 15, 30 and 60 minutes after dosing.

A very slight decrease in serum iron (8.6%) was observed at 5 minutes after dosing. By 15 minutes, serum iron was again comparable to pre-dose values. The only other statistically significant change was a slight decrease in plasma prothrombin time (6.3%) at 60 minutes after dosing. Because of the direction of the change in prothrombin time, this small difference was not considered to represent an adverse effect on hemostasis.

Bleeding times, blood clotting times, and activated partial thromboplastin times were not changed from pre-dose values.

Compatibility with Human Erythrocytes
Aliquots of buffered saline (for saline blank and 100% hemolysis) and the ProHance® solution were each mixed with heparinized whole blood from human volunteers in dilutions of 1:10 and 1:20. The samples were incubated for 45 minutes at 37°C, with gentle inversion at approximately 15 minute intervals. The ProHance® formulation did not demonstrate any potential for hemolysis at either dilution.

Arterial Irritation in Rabbits

The ProHance® formulation (0.5 mL) was injected retrograde into the central artery of one ear of 2 male and 2 female rabbits. A similar control group received 0.5 mL of 0.9% sterile saline.
Injection sites were examined 1, 2, 3, 5, 9, 16 and 21 days after administration. Slight redness and small hematomas were observed for up to five days in both groups. The intensity of the observations with ProHance® were generally comparable to, or less than, that seen in the control group.

Antipyretic Activity in Rabbits

The ProHance® formulation was given intravenously to three groups of four male rabbits each at 0.25, 0.5 and 1.0 mmol/kg one hour after a 1 *µg/kg* intravenous dose of *E. coli* lipopolysaccharine (LPS). A control group received 2 mL/kg of 0.9% saline one hour after the . same dose of LPS. Rectal temperatures recorded before treatment and for 6 hours post-dosing showed no significant differences between treated and control rabbits.

TOXICOLOGY

Acute Toxicity

Single intravenous doses of 1.25, 2.5, 5, 7, 10 and 14 mmol/kg of gadoteridol (as the ProHance® formulation) were injected to groups of 10 male and 10 female Charles River CD-l mice at a rate of 0.02 mL/second. The maximum nonlethal dose was 7 mmol/kg (70 times the clinical dose). The maximal no-e£fect dose was 1.25 mmol/kg. The estimated LD_{50} was 10.7 mmol/kg in males and 13.6 mmol/kg in females. Decreased activity was observed in surviving animals at doses of 2.5 mmol/kg or more. Ataxia, convulsions, collapse and bloody exudate from the nares were seen in mice that died. All death occurred within 6 minutes. Surviving mice appeared normal 24 hours after dosing.

Single intravenous doses of 2.5, 5 and 10 mmol/kg of gadoteridol (as the ProHance® formulation) were given to groups of 10 male and 10 female Sprague Dawley rats at a rate of 0.1 mL/second. No lethality was observed even at the highest dose (100 times the clinical dose). Slower respiration rate and decreased activity occurred in a dose-related manner. The maximal no-effect dose was 2.5 mmol/kg in males and 5 mmol/kg in females.

Multidose Studies

Mice

Groups of 6 males and 6 female Charles River CD-l mice were given daily intravenous doses of 1.5, 3 or 6 mmol/kg (as the ProHance® formulation) for two weeks. A similar group which received 0.9% saline at 12 mL/kg i.v. daily served as a control. Criteria for evaluation included survival, body-weight changes, excreta, physical condition, behaviour, clinical laboratory test results, and gross and histopathologic examinations of tissues.

One male died shortly after the first dose at 6 mmol/kg. Signs prior to death included periods of inactivity and marked body tremors. At necropsy, the only gross lesion was discoloration of the tail at the injection site.

Within minutes after administration of the first daily dose, all intermediate and high dose mice showed periods of decreased activity, lasting approximately 30 minutes. High-dose mice also showed decreased activity after the second and third doses.

During the second week, intermediate and high dose mice showed slight decreases in urine pH and slight increases in urine specific gravity. At the end of the second week, slight decreases in serum total protein (albumin) were evident in high dose mice. There were no other treatment-related adverse effects during the dosing period.

At necropsy, red discoloration and some ulcers were noted at the tail injection sites for some animals in each group, including controls. Histologically, inflammation at the injection sites was present at a slightly higher incidence in the higher dose animals. The only other statistically significant histopathologic finding was a decrease in the incidence of mineralization of the tracheal cartilaginous rings in intermediate and high dose males.

Rats

Recent studies conducted in healthy rats injected repeatedly with linear or macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighed hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP) could not be seen in the animals. No changes in signal intensities in either DCN or GP were observed for the macrocyclic GBCAs.

Quantitative results using mass spectrometry demonstrated that the total gadolinium concentrations were significantly higher with the linear GBCAs than with the macrocyclic GBCAs. These studies reported no abnormal behavioral changes suggestive of neurological toxicity.

Dogs

The ProHance® formulation was administered intravenously to three groups of beagle dogs, once daily for two weeks, at gadoteridol doses of 0.25, 0.6, and 1.5 mmol/kg. An additional group of dogs, given 0.9% saline intravenously at 3 mL/kg, served as control. Each group consisted of two male and two female dogs. Criteria for evaluation included survival, bodyweight changes, food and water consumption, excreta, physical condition, behavior, electrocardiography, ophthalmoscopy, results of clinical-laboratory tests, and gross and histopathologic examinations of tissues from all animals.

Most of the dogs given 0.6 and 1.5 mmol/kg had slight subcutaneous thickening at the injection sites. Bleeding times, determined about 1 hour after administration of a daily dose during the first week, were slightly prolonged in the intermediate and high dose groups; however, dogs given 0.25 mmol/kg daily were not affected. During the second week, bleeding times were slightly prolonged at 0.25 mmol/kg and moderately prolonged in the groups given 0.6 and 1.5 mmol/kg. There were no changes in plasma prothrombin

times or blood clotting times, determined at the same time points. There were no other treatment-related changes during the dosing period.

No treatment-related changes in organ weights were observed and there were no treatment-related gross or microscopic lesions at any dose level.

REPRODUCTION STUDIES

Teratology - Rats

The ProHance® formulation was administered intravenously to four groups of at least 30 pregnant rats each (F_0 generation) at gadoteridol dose levels of 0.375, 1.5, 6 and 10 mmol/kg.These dose levels represented dose volumes of 0.75, 3, 12 and 20 mL of formulation/kg, respectively. The doses were based on maternal body weight on day 6 of gestation and were administered once daily from day 6 through day 17 of gestation (day of mating = 0). Two similar groups of rats were administered sterile 0.9% sodium chloride solution at dose volumes of 12 or 20 mL/kg on the same schedule and served as controls. At least 20 pregnant F_0 rats per group were subjected to caesarean section on day 20 of gestation.

The number of corpora lutea, resorptions, and live and dead fetuses were determined in each dam, and the anogenital
distance, placental weight, body weight, and sex were determined in each live fetus. All live fetuses were examined for the presence of gross external abnormalities. In addition, half of the live fetuses in each litter were examined for skeletal defects and degree of skeletal ossification; the remaining fetuses were examined for the presence of soft-tissue defects. All dead fetuses were examined for the presence of gross external abnormalities and the gestational age at time of death was estimated. At least 10 pregnant F_0 rats per group were allowed to deliver naturally and nurse their offspring until weaning. All F_1 pups at birth (day 0 of lactation) were weighed and examined for the presence of gross external abnormalities. After weighing, the pups were randomly culled to eight pups per litter. The postnatal evaluation of the F_1 rats included viability, physical development, neuromuscular function, sensory function, reflexive behavior, maze-learning ability, level of spontaneous activity, and reproductive capacity.

The following changes were noted in F_0 dams subjected to caesarean section: one dam administered 10 mmol/kg died and the death was attributed to gadoteridol; maternal weight gain and daily food consumption during gestation were reduced at 10 mmol/kg; absolute spleen weight was increased at 1.5 mmol/kg and relative spleen weight was increased at all dose levels; absolute and relative kidney weights were increased at 6 and 10 mmol/kg; absolute and relative liver weights were increased at 10 mmol/kg; and absolute and relative heart weights were reduced at 10 mmol/kg. The only maternal clinical sign attributed to gadoteridol was an increase in the incidence of urine staining at 10 mmol/kg. At caesarean delivery, the incidences of embryonal and fetal deaths, fetal body weights, placental weights, and anogenital distances in fetuses were comparable among all groups. A number of major craniofacial malformations were noted at 10 mmol/kg. Similar craniofacial abnormalities were observed in control fetuses from dams administered an equal volume of saline and the incidence of the malformations in these animals was statistically comparable to the high-dose group. For the above reasons, the malformations in the treated group were not attributed to the administration of gadoteridol,

but appeared to be due to a dose-volume effect.

In F_0 dams that delivered naturally, absolute and relative spleen weights were increased and absolute and relative uterine weights were decreased at 10 mmol/kg. The only maternal clinical sign attributed to gadoteridol was an increase in the incidence of urine staining at 10 mmol/kg.

The length of gestation, the gestation index (% of litters case alive), the birth index (% of live newborns), and the sex ratio of newborns were statistically comparable among all groups. The incidence of gross external abnormalities in pups at birth was comparable in all groups, and no abnormality was attributed to gadoteridol.

Sections of kidneys, liver, and spleen from some F_0 dams in each group were examined for microscopic changes. Significant treatment-related multifoca1, cytoplasmic vacuolation of renal cortical tubular epithelial cells was observed in the 6 and 10 mmol/kg groups in both caesarean- sectioned females and females scheduled for natural parturition.
However, the renal tubular cell vacuolation was less severe in the 6 mmol/kg females scheduled for natural parturition than in those for caesarean section, suggesting reversibility of this change in animals treated with 6 mmol/kg. The severity of the renal lesions was similar in caesarian-sectioned and natural parturition females at 10 mmol/kg. Mild to moderate, multifoca1 vacuolation of hepatocytes was observed in the group scheduled for natural parturition, and these changes were most likely treatment-related. Livers from females scheduled for caesarean section were not examined.

In the postnatal evaluation of the F_1 generation, the only adverse finding attributed to gadoteridol was an increase in the level of spontaneous horizontal (ambulation) activity in males at 6 and 10 mmol/kg.

Rabbits
A 1.0 M formulation of gadoteridol was administered intravenously to three groups of 15 inseminated rabbits each, at daily gadoteridol doses of 0.4, 1.5 and 6.0 mmol/kg. The doses, based upon body weight on day 6 of gestation, were administered once daily from day 6
through day 18 of gestation (day of insemination = 0). A similar group of 15 rabbits was administered sterile 0.9% saline on the same schedule and served as control. On day 29 of gestation, the does were subjected to caesarean section, and the number and condition of all implantations were determined. All live fetuses delivered by caesarean section were examined for gross external, soft-tissue, and skeletal abnormalities; all dead fetuses were examined for gross external and internal (unless autolyzed) abnormalities.

A total of 14, 15, 13 and 14 does were pregnant in control, low, intermediate, and high-dose groups, respectively. All pregnant does survived to their scheduled date of caesarean section, except one doe in the low-dose and three does in the high-dose groups that aborted, one doe in the high-dose group that delivered early, and three does in the high-dose group that died.
The incidence of does in the high-dose group that died or delivered spontaneously (46.7%) was significantly greater than control ($P < 0.01$) indicating that a daily gadoteridol dose of 6 mmol/kg was maternotoxic.

In pregnant does that survived to caesarean section, total maternal weight gain, maternal carcass weight at caesarean section, maternal carcass weight gain, gravid uterine weight, and maternal food consumption were statistically comparable among all groups. At caesarean section, the mean numbers of implants per dam for control through high-dose groups were 5.6, 5.0, 5.1, and 5.9 respectively; the incidences of resorptions were 15.4, 5.7, 9.1 and 19.5 percent; and the incidences of fetal deaths were 1.5, 0, 1.7 and 0 percent. All of these values were statistically comparable and within expected limits. Fetal body weights and placental weights also were statistically comparable among all groups. Finally, no major malformations were observed in fetuses and the incidences of gross, soft-tissue, and skeletal findings were comparable among all groups.

MUTAGENICITY STUDIES

The ability of the ProHance® formulation to induce micronuclei in bone marrow polychromatic erythrocytes of ICR mice was evaluated. The formulation was given by intravenous injection of gadoteridol doses of 0.5, 1.5, and 5.0 mmol/kg. The animals were dosed with the test article and were killed 24, 48, and 72 hours after dosing for extraction of the bone marrow. Ten animals (five males and five females) were randomly assigned to each dose/kill time group.

Negative and positive control groups killed 24 hours after dosing were included in the assay. The ProHance® formulation did not induce a significant increase in micronuclei in bone marrow polychromatic erythrocytes under the conditions of this assay and is considered negative in the mouse bone marrow micronucleus test.

The ability of the ProHance® formulation to induce forward mutations at the thymidine kinase (TK) locus in the mouse lymphoma L5178Y cell line was evaluated. In the preliminary cytotoxicity assay, cells were exposed to the test material for four hours in the presence and absence of rat liver S9 metabolic activation. The test material remained in solution and caused no adverse pH effects in culture medium up to the maximum applied concentration of 50.0 mM.

The test material was nontoxic under both test conditions. In the mouse lymphoma assay, *in vitro* treatments with the test material did not induce any significant increases in mutant frequency at the TK locus. Two independent trials were performed for both nonactivation and S9 metabolic activation conditions. Each trial included six or seven dose levels that ranged from 1.0 mM or 5.0 mM to 50.0 mM. All dose levels survived treatment without toxicity. The ProHance® formulation was evaluated as negative for inducing forward mutations at the TK locus in L5178Y mouse lymphoma cells under nonactivation and S9 metabolic activation conditions.

The ability of the ProHance® formulation to induce chromosomal aberrations in Chinese hamster ovary (CHO) cells with and without metabolic activation was evaluated. A half-log series of concentrations of 0.0003 mM to 10.0 mM was tested in the range finding assays with and without metabolic activation. There was no evidence of toxicity or cell cycle delay at any of the concentrations analyzed. Duplicate cultures of CHO cells were incubated with concentrations of 1.00 to 10.0 mM of the test article in the aberrations assays with and without activation. No significant increase in chromosomally aberrant cells was observed at any of the concentrations analyzed. The ProHance® formulation is considered negative for inducing chromosomal aberrations in Chinese hamster ovary cells under both nonactivation and activation conditions.

The ProHance® formulation was examined for mutagenic activity in Bacterial Reverse Mutation assays using Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100, and Escherichia coli strain, WP2uvrA-. The assays were conducted using three plates per dose level, at doses of 0.0025 to 0.15 mmol per plate, in the presence and absence of a metabolic activation system. The assays employing Salmonella typhimurium strains and the Escherichia coli assay were both performed twice. The ProHance® formulation did not exhibit genetic activity in these assays and was not mutagenic under these test conditions according to assay criteria.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ProHance®
Gadoteridol injection

Read this carefully before you start taking **ProHance** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ProHance**.

Serious Warnings and Precautions

- ProHance will be given to you by a healthcare professional called a radiologist who has experience in magnetic resonance imaging (MRI) procedures.

- As with other contrast medications similar to ProHance, there is a possibility of allergic reactions. Serious allergic reactions can occur after you receive ProHance. These reactions can be fatal. Get immediate medical help if you get any of the following symptoms: difficulty breathing, hives, itching, rash, runny nose, swelling of your face, tongue or throat or a very fast heartbeat. You may be observed by your healthcare professional for several hours after you receive ProHance. This will be done if you have had an allergy or reaction to a medicine in the past.

- Tell your healthcare professional if you have a condition called a hemolytic anemia including sickle cell anemia. If you have one of these conditions ProHance could make your blood condition worse. This medication has not been studied in individuals with these conditions.

- If you have kidney problems you could get a rare disease called **Nephrogenic Systemic Fibrosis (NSF)** after receiving medicines such as ProHance. With NSF, the skin becomes thickened, coarse and hard, which makes bending of the joints difficult. NSF may spread to other parts of your body and even cause death. Patients with kidney problems should not use ProHance unless your health care professional believes the possible benefits outweigh the potential risks. Get immediate medical help if you get any of the following symptoms after receiving ProHance:
    - Swelling, hardening and tightening of your skin
    - Red or dark patches on your skin
    - Burning or itching of your skin
    - Yellow spots on the whites of your eyes
    - Stiffness in your joints, problems moving or straightening arms, hands, legs or feet
    - Pain deep in your hip bone or ribs
    - Muscle weakness

  Your healthcare professional will monitor your health after administering ProHance, if you are at risk for getting NSF. They might give you a lower dose and wait longer before giving you ProHance again.

What is ProHance used for?

ProHance is a contrast agent used for magnetic resonance imaging (MRI).

In adults and children 2 years of age and older:

- It is used for MRI of the brain, spine and surrounding tissues.

In adults:

- It is also used for MRI of the head and neck.

How does ProHance work?
ProHance makes your tissues brighter. This allows your healthcare professional to see any abnormal tissues during MRI procedures.

What are the ingredients in ProHance?
Medicinal ingredients: Gadoteridol
Non-medicinal ingredients: calteridol calcium, hydrochloric acid, tromethamine, sodium hydroxide, water for injection

ProHance comes in the following dosage forms:
ProHance is supplied as a solution for injection containing gadoteridol 279.3 mg/mL

Do not use ProHance if:
- you are allergic to gadoteridol or to any of the non-medicinal ingredients in ProHance.

ProHance should not be used in children less than 2 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ProHance. Talk about any health conditions or problems you may have, including if you:

- have had seizures in the past
- have kidney problems
- have had allergies in the past
- have had an allergic reaction to a medicine in the past
- have a condition called a hemolytic anemia including sickle cell anemia
- are pregnant or are planning to become pregnant
- are breastfeeding or are planning to breastfeed

Other warnings you should know about:

Accumulation of gadolinium in the brain:

Recent information shows that gadolinium (as in ProHance) may build up in the brain after multiple uses and:

The effect on the brain is unknown right now.

Your doctor will:

- Carefully consider whether to use repeated doses
- Use the lowest dose

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take ProHance:

- ProHance will be given to you by a healthcare professional.
- It will be infused directly into your vein.
- It will be given to you before or during your MRI procedure.
- Follow all instructions given to you by your healthcare professional.

Usual dose:

- Your healthcare professional will decide how much ProHance you will receive.
- The dose you receive will be based on the procedure you are getting and your weight.
- Your healthcare professional will use the lowest dose that is possible.

Overdose:

If you think you have taken too much ProHance, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using ProHance?

Side effects may include:

- altered sense of taste
- nausea
- pain and redness at injection site
- feeling flushed
- vomiting
- anxiety
- inflammation of the gums
- headache
- dizziness
- chest pain
- abnormal sensation in the skin (tingling, prickling or numbness)
- dry mouth
- abdominal pain
- fever
- sweating
- slow heart beat
- diarrhea
- ringing in the ears
- high blood pressure

- difficulty swallowing
- feeling sick
- lack of control of urination
- temporary change in voice
- neck stiffness
- cough
- shaking

These are not all the possible side effects you may feel when taking ProHance. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Serious allergic reactions that can be fatal: difficulty breathing, hives, itching, rash, runny nose, swelling of your face, tongue or throat, very fast heartbeat.			X
Low blood pressure: dizziness, fainting.			X
Nephrogenic systemic fibrosis (NSF) in patients with kidney disease**:** thick, hard skin (sometimes looks like orange peels), decreased movement and flexibility in arms or legs, muscle weakness, joint and muscle pain.			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
ProHance should be stored at room temperature (15 to 30°C) and protected from light.

Keep out of reach and sight of children.

If you want more information about ProHance:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.braccoimaging.com, or by calling 1-800-465-5820.

This leaflet was prepared by Bracco Imaging Canada

Last Revised 09-MAR-2018