ProHance®

(Gadoteridol) Injection, 279.3 mg/mL

**STABILITY. SAFETY. EFFICACY.**

MR Suite


GBCA = Gadolinium-based contrast agent.

*Source: IQVIA DDD: November 2019.

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# MultiHance® (gadobenate dimeglumine) injection, 529 mg/mL and ProHance® (Gadoteridol) Injection, 279.3 mg/mL

**Indications and Usage for MultiHance® (gadobenate dimeglumine) injection, 529 mg/mL:**
MultiHance (gadobenate dimeglumine) injection, 529 mg/mL is a gadolinium-based contrast agent 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 and
- Magnetic resonance angiography (MRA) to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease

**Indications and Usage for ProHance® (Gadoteridol) Injection, 279.3 mg/mL:**

CENTRAL NERVOUS SYSTEM
ProHance (Gadoteridol) Injection, 279.3 mg/mL 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 (Gadoteridol) Injection, 279.3 mg/mL is indicated for use in MRI in adults to visualize lesions in the head and neck.

**IMPORTANT SAFETY INFORMATION for MultiHance and ProHance:**

**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/ProHance dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration. (see ***WARNINGS***)

**MultiHance (gadobenate dimeglumine) injection, 529 mg/mL**
Anaphylactic and anaphylactoid reactions have been reported, involving cardiovascular, respiratory, and/or cutaneous manifestations ranging from mild to severe. The possibility of a reaction should always be considered, especially in those patients with a history of a known clinical hypersensitivity or a history of asthma or other allergic disorders. Trace amounts of gadolinium may remain for months or years in the body organs including bone (highest concentration), brain, liver, spleen, kidneys and skin. Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of retention in skin and other organs have been established in patients with impaired renal function. Minimize repetitive GBCA imaging studies, particularly close spaced studies when possible.

**ProHance (Gadoteridol) Injection, 279.3 mg/mL**
As with all paramagnetic agents, caution should be exercised in patients with deoxygenated sickle erythrocytes and renal insufficiency with or without hepatic impairment. The possibility of a reaction, including serious, life threatening, or fatal, anaphylactic or cardiovascular reactions, or other idiosyncratic 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 disorders. Trace amounts of gadolinium may remain for months or years in the body organs including bone (highest concentration), brain, liver, spleen, kidneys and skin. Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of retention in skin and other organs have been established in patients with impaired renal function. Minimize repetitive GBCA imaging studies, particularly close spaced studies when possible.

**Please see full Prescribing Information and Patient Medication Guide for additionalimportant safety information for/ regarding MultiHance (gadobenate dimeglumine) injection, 529 mg/mL at** https://www.braccoimaging.com/us-en/products/magnetic-resonance-imaging/multihance

**Please see full Prescribing Information and Patient Medication Guide for additional important safety information for/ regarding ProHance (Gadoteridol) Injection, 279.3 mg/mL at** https://www.braccoimaging.com/us-en/products/magnetic-resonance-imaging/prohance

**You are encouraged to report negative side effects of prescription drugs to the FDA. Visit** www.fda.gov/safety/medwatch/default.htm **or call 1-800-FDA-1088.**

MultiHance® (gadobenate dimeglumine) is manufactured for Bracco Diagnostics Inc. by BIPSO GmbH – 78224 Singen (Germany) and by Patheon Italia S.p.A., Ferentino, Italy.
ProHance® (Gadoteridol) is manufactured for Bracco Diagnostics Inc. by BIPSO GmbH – 78224 Singen (Germany).

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## ProHance® (Gadoteridol) Injection, 279.3 mg/mL

# At the Forefront of MRI

The ProHance Triad of Benefits provides assurance for patients and referring physicians.

- Minimal Gd retention[2-5,*]
- No medically confirmed unconfounded NSF cases[6]
- Comparable tolerability to other GBCAs[7-13]

**ProHance introduced the first macrocyclic GBCA in the U.S. with high stability.**

ProHance®
(Gadoteridol) Injection, 279.3 mg/mL
STABILITY. SAFETY. EFFICACY.

NSF = nephrogenic systemic fibrosis.
*Based on animal studies exploring gadolinium retention in the brain and kidneys among macrocyclic agents.[2-4]
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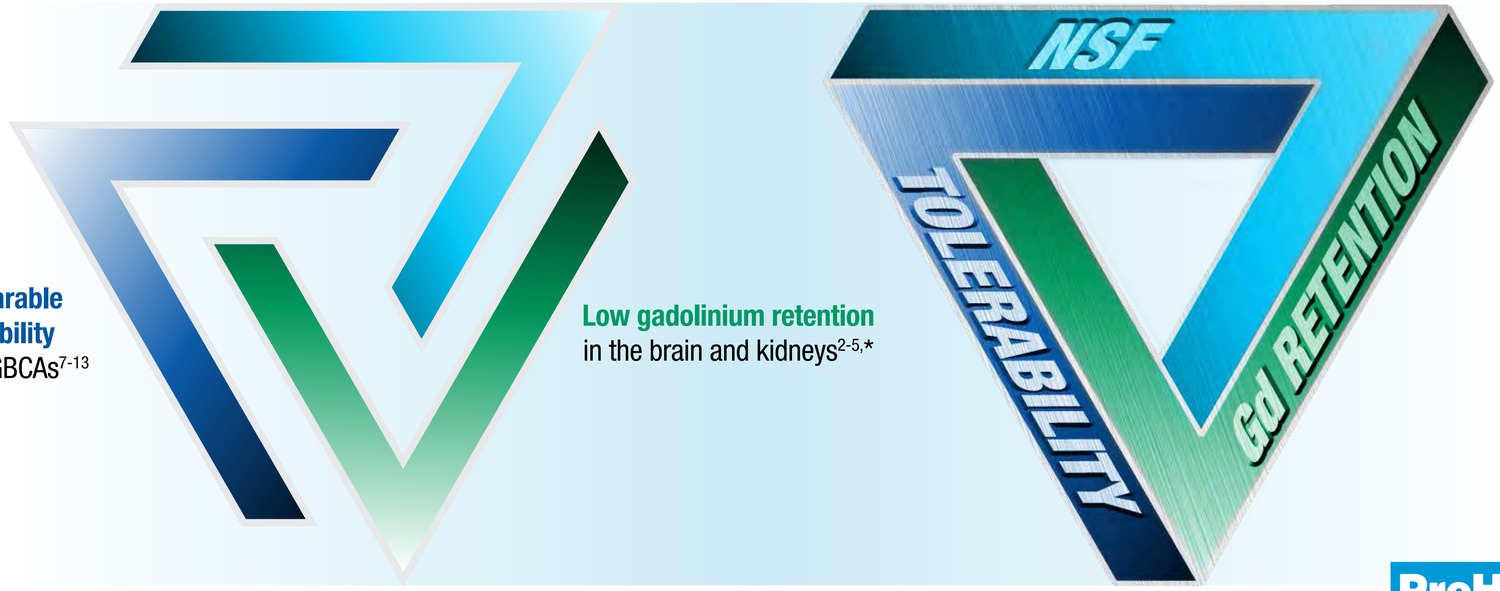
ProHance® (Gadoteridol) Injection, 279.3 mg/mL

# Triad of Benefits

## Enhancing diagnostic MRI

The ProHance Triad of Benefits provides assurance for patients and referring physicians in need of a GBCA.

**No medically confirmed unconfounded cases of NSF**
in more than 28 million doses worldwide[6,14]




**Comparable tolerability**
to other GBCAs[7-13]

**Low gadolinium retention**
in the brain and kidneys[2-5,*]

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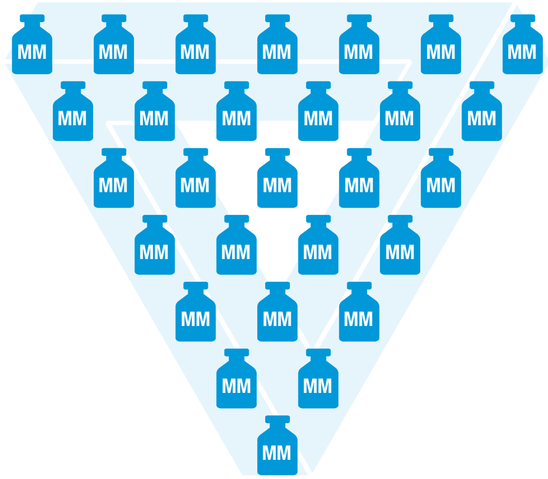
ProHance® (Gadoteridol) Injection, 279.3 mg/mL

# No Medically Confirmed Unconfounded NSF Cases[6]

## 28 million doses worldwide[14]


Among macrocyclic agents,
**ProHance has no medically confirmed unconfounded reports of NSF in the literature.[6]**




ProHance is classified as a Group II Agent by the American College of Radiology (ACR)[15,*]
**with greater than 28 million doses administered worldwide.[14]**

To date, the vast majority of NSF cases have been shown to occur following the administration of a standard-relaxivity, linear GBCA, and few medically confirmed unconfounded (single-agent) cases of NSF have been described following use of a macrocyclic agent.[15]

MM = 1 million doses.

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*ACR classifies Group II Agents as those with few, if any, medically confirmed unconfounded cases of NSF.

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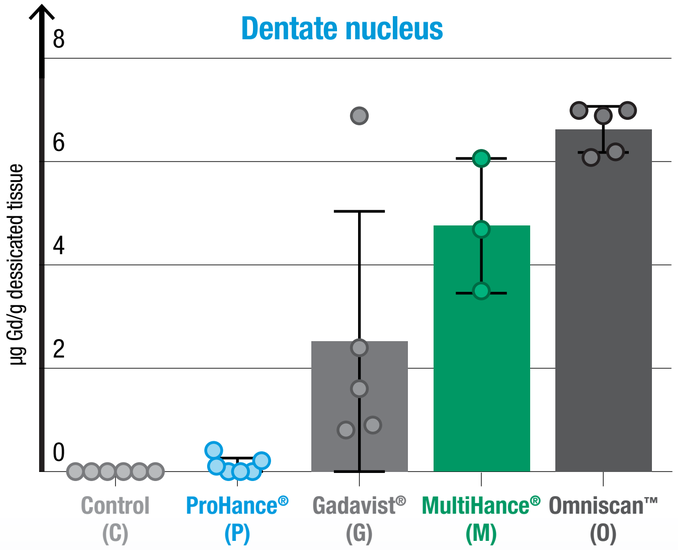
## ProHance® (Gadoteridol) Injection, 279.3 mg/mL

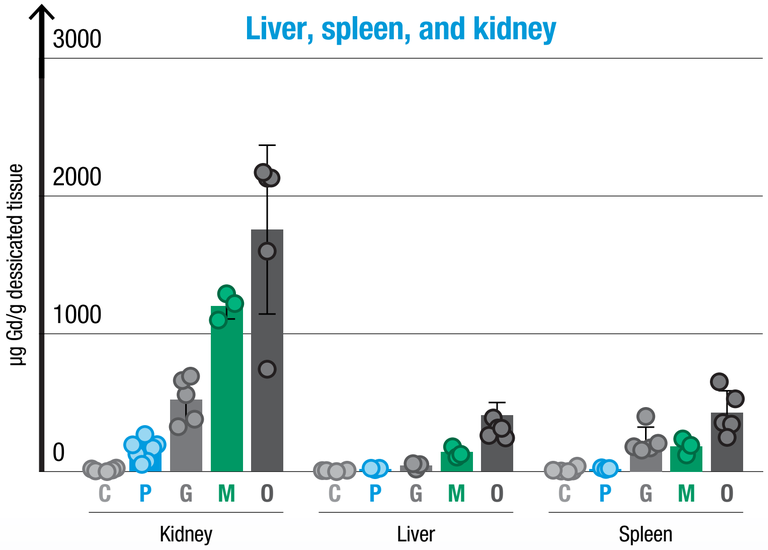
# Low Gadolinium Retention

## Brain, kidney, liver, and spleen[2]

Data from an animal study, using ICP-MS, indicates…

**ProHance demonstrated lower Gd retention at day 7 in the brain, kidney, liver, and spleen.[2]**




Adapted from McDonald et al. *Radiology.* 2017[2]

> "Macrocyclic contrast agent deposition is not universally lower than linear agents, with some macrocyclic agents apparently demonstrating higher tissue gadolinium deposition than what has been previously described in skin biopsy samples and recent reports of T1-weighted signal intensity changes.[2]"
>
> **—McDonald et al. 2017**

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ICP-MS = inductively coupled plasma mass spectrometry.

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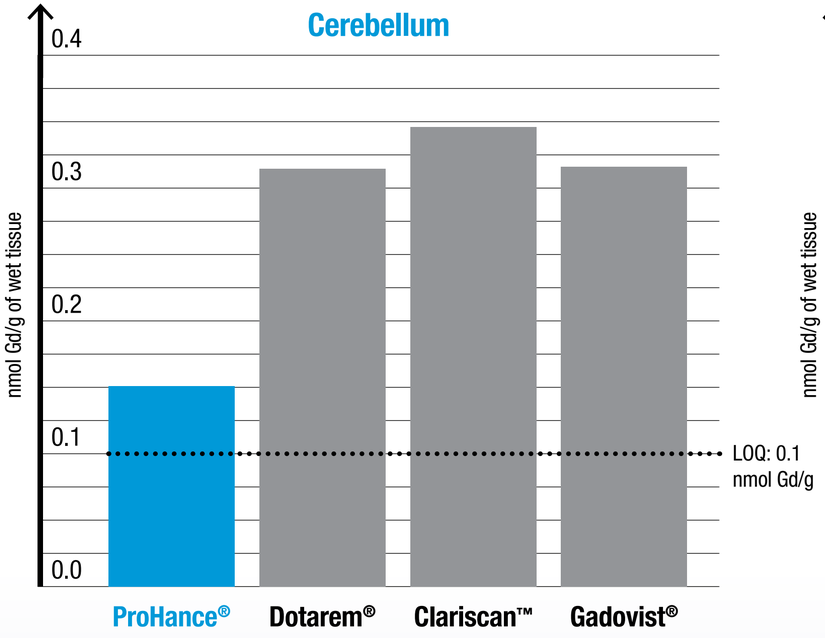
## ProHance® (Gadoteridol) Injection, 279.3 mg/mL

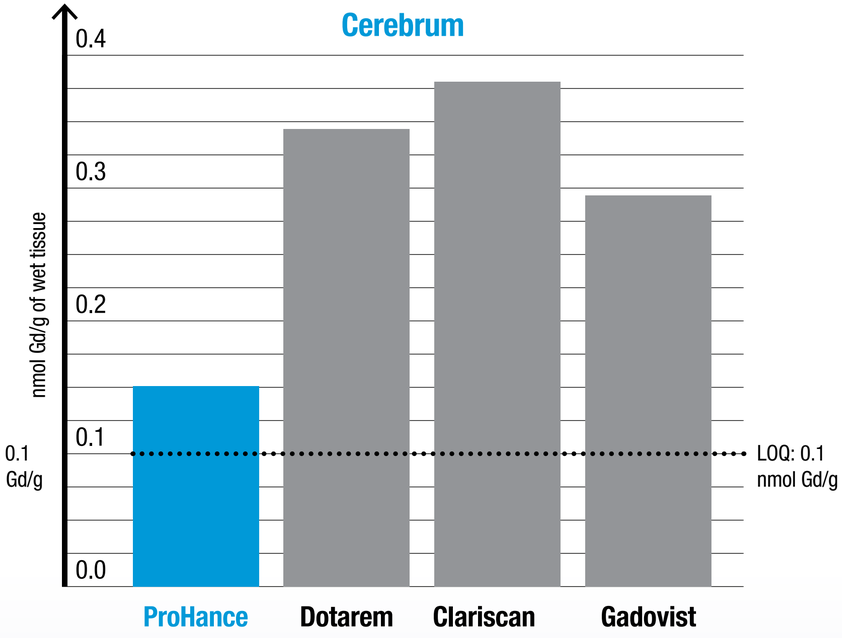
# Low Gadolinium Retention

## Cerebellum and cerebrum[3,4]

Data from the Bussi animal study, using ICP-MS, indicates…

**ProHance outperformed all other macrocyclic agents with lower Gd retention in the brain, kidneys, and liver at up to four weeks.[3]**




Adapted from Bussi et al. *Insights into Imaging.* 2020.

Gadolinium retention is seen following the administration of any of the GBCAs but there are differences among linear and macrocyclic agents.[2-5,16,17]

- Linear agents have greater levels of Gd retention than macrocyclic agents
- Levels of Gd retention can vary among macrocyclic agents

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Gadovist is the brand name in Europe for Gadavist® (Gadobutrol).

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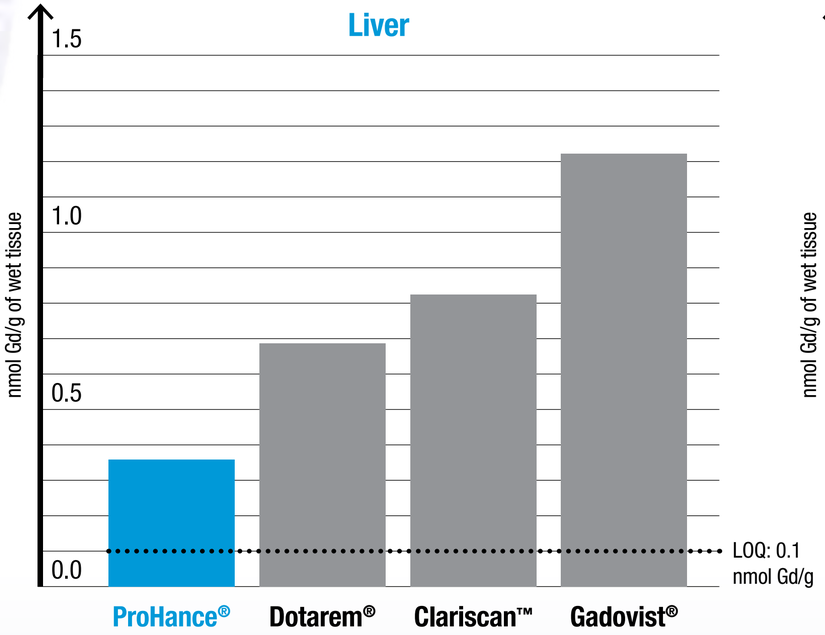
## ProHance® (Gadoteridol) Injection, 279.3 mg/mL

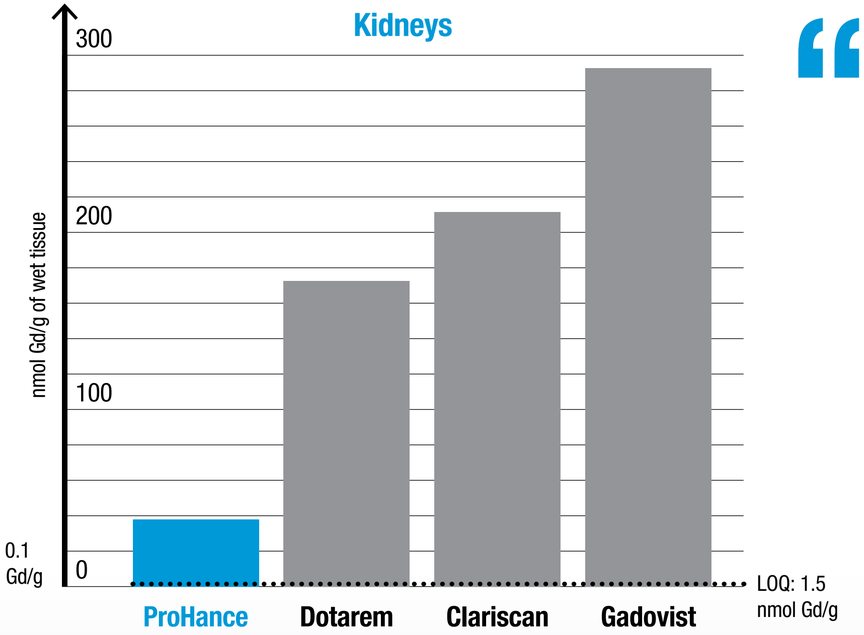
# Low Gadolinium Retention

## Liver and kidneys[3,4]

Data from the Bussi animal study, using ICP-MS, indicates…

**ProHance outperformed all other macrocyclic agents with lower Gd retention in the brain, kidneys, and liver at up to four weeks.[3]**




Adapted from Bussi et al. *Insights into Imaging.* 2020.

> "[ProHance] has a low molecular 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 [Gadovist] and [Dotarem].[3]"
>
> **—Bussi et al. 2020**

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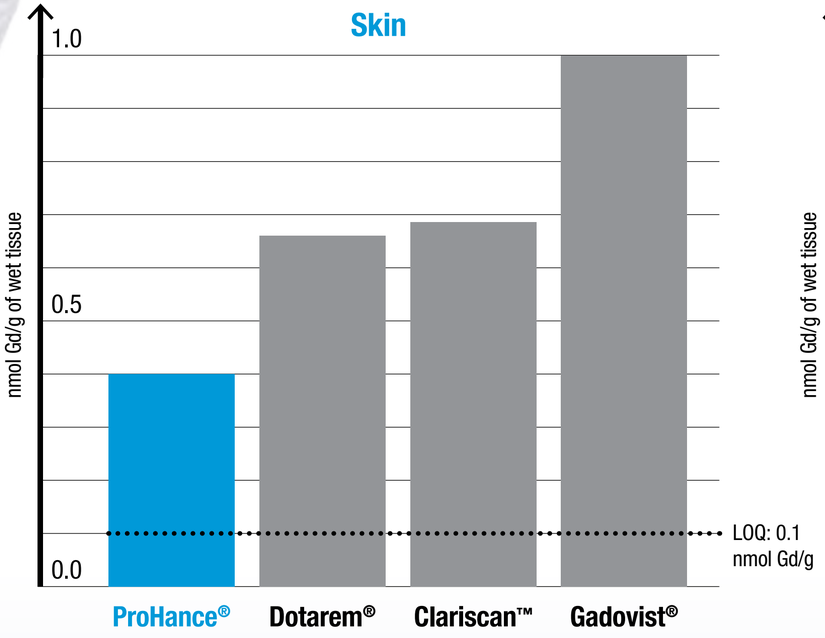
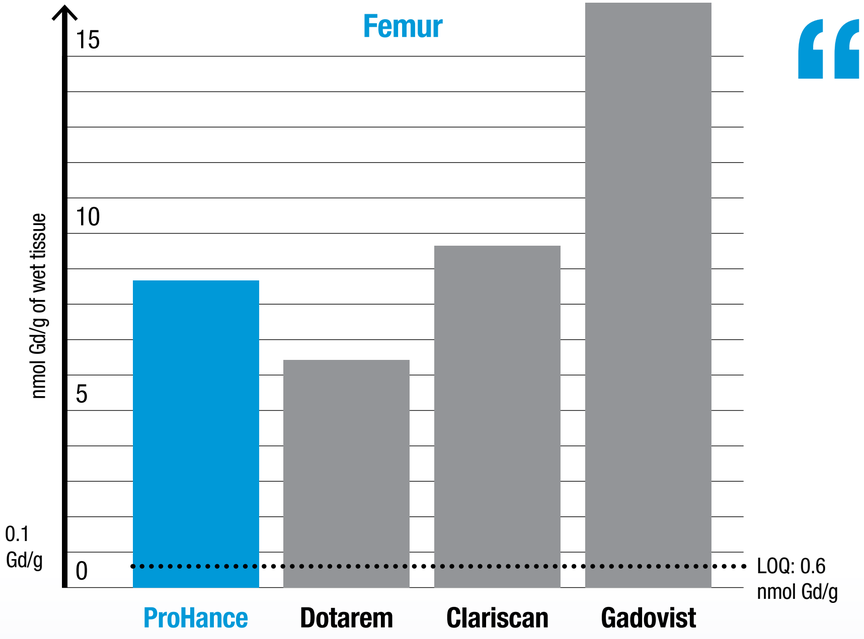
# Low Gadolinium Retention

## Skin and bone[3,4]

Data from the Bussi animal study, using ICP-MS, indicates…

**ProHance outperformed all other macrocyclic agents with lower Gd retention in the brain, kidneys, liver, and skin and was among the lowest in bone at up to four weeks.[3]**




Adapted from Bussi et al. *Insights into Imaging.* 2020.

> "Considerably lower levels of retained Gd in brain and soft body tissues… after the administration of ProHance… than after equivalent cumulative doses of not only Dotarem and Gadovist but also the newly marketed GBCA, Clariscan administered under identical conditions.[3]"
>
> **—Bussi et al. 2020**

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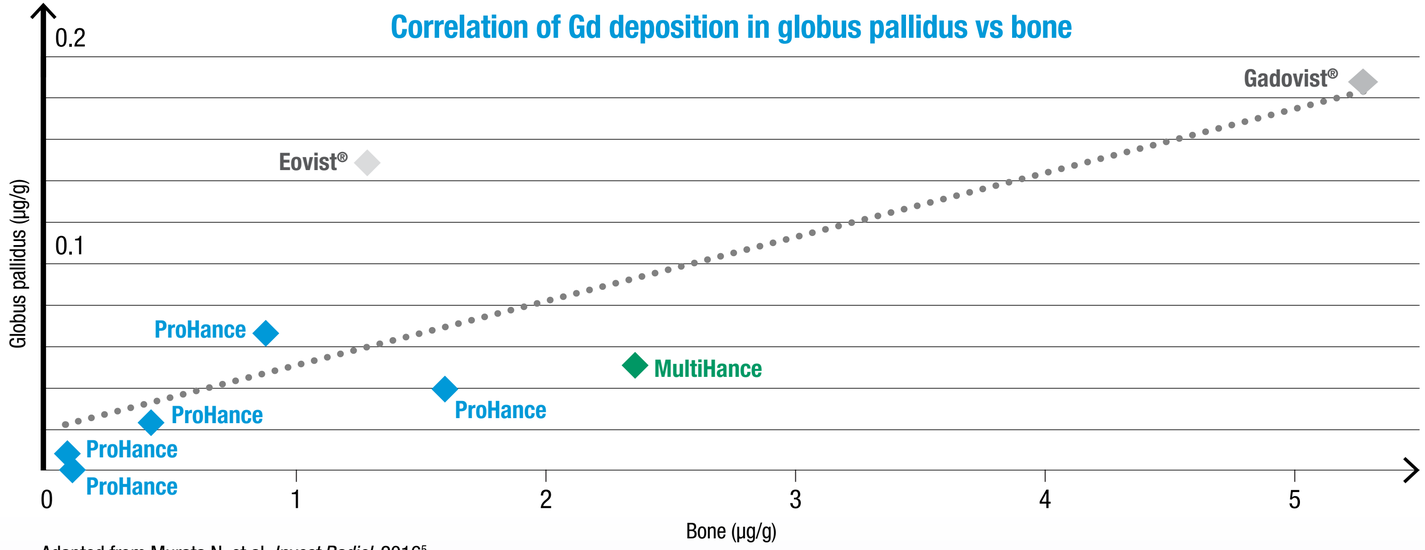
# Low Gadolinium Retention

## Postmortem human brain[5]

Human data from a small-scale tissue sampling study using ICP-MS indicates that…

**ProHance administration results in low residual gadolinium in the brain[5]**




Adapted from Murata N, et al. *Invest Radiol.* 2016[5]

> "Residual gadolinium has been found within the brain tissue of patients who received multiple doses of GBCAs over their lifetimes... Fortunately, there have been no reports to date to suggest these deposits are associated with histologic changes that would suggest neurotoxicity.[15]"
>
> **—ACR: 2018 position statement on GBCAs**

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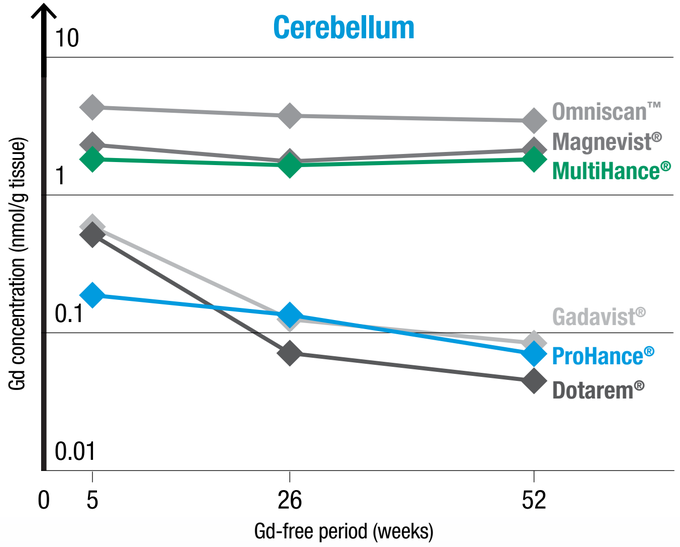
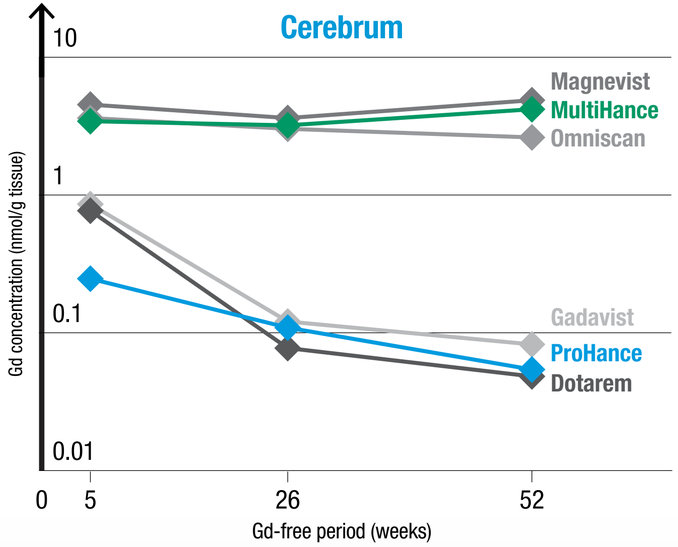
# Rapid Gadolinium Clearance

## Cerebellum and cerebrum[18]

Data from an extensive animal study, using ICP-MS, indicates…

**Faster and greater elimination of ProHance at early timepoint (5 weeks) after last injection compared to all other macrocyclic GBCAs.[18]**




Adapted from Jost G, et al. *Radiology*. 2018[18]

> "Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and we have concluded that the benefit of all approved GBCAs continues to outweigh any potential risks.[19]"
>
> **—FDA: 2018 position on gadolinium retention**

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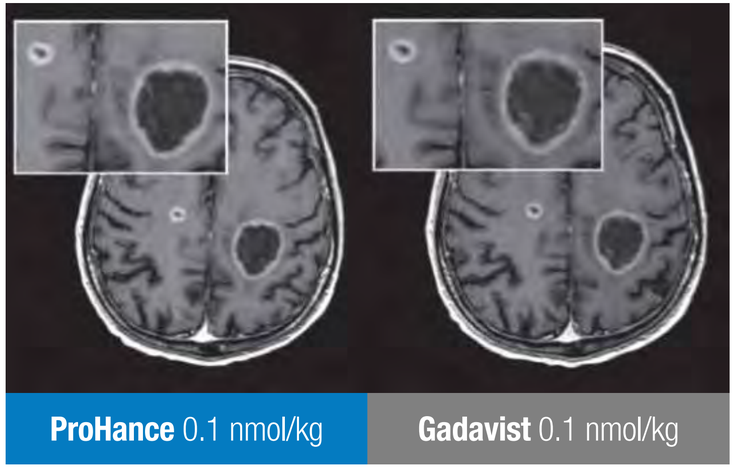
# Proven Efficacy

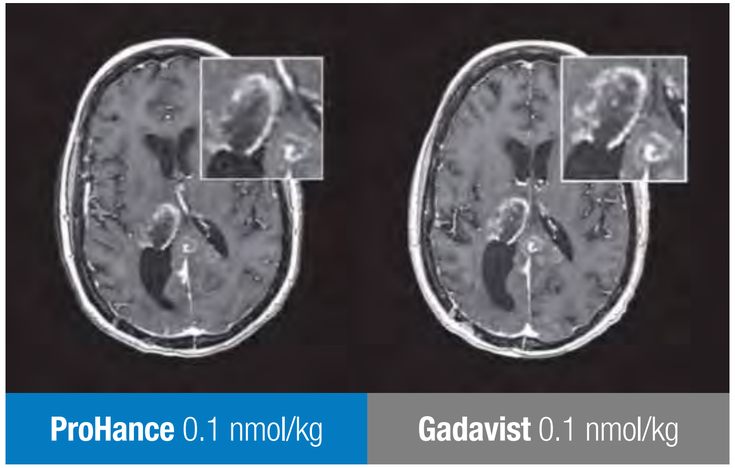
## Performances of Gadavist® and ProHance for visualization parameters are similar[10,20]

Detection and characterization of CNS lesions with ProHance (gadoteridol) was non-significantly different when compared to Gadavist (gadobutrol)…

**Minimal differences in relaxivity between ProHance and Gadavist do not demonstrate clinical differences in routine neuroradiological applications of CNS MRI.**[10,20]




61-year-old man with brain metastases from primary lung cancer. Two lesions clearly seen in both exams show no differences in contrast enhancement or in the morphology of lesions.[20]




51-year-old woman with glioblastoma multiforme. Rim-enhancing mass in right thalamus with extension into the posterior interhemispheric region is clearly seen in both examinations. No differences in contrast enhancement or in the morphology of lesions are apparent.[20]

Adapted from Maravilla KR, et al. *AJNR Am J Neuroradiol.* 2015[20]

The TRUTH study showed no significant difference by any reader for any of the 5 endpoints:[20]

- Global diagnostic preference
- Lesion border delineation
- Definition of disease extent
- Visualization of lesion internal morphology
- Lesion contrast enhancement

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These are representative images from reference studies, individual results may vary.

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# Tolerability of ProHance

## Triple dose approved[7]

ProHance is well tolerated, with low overall rates of adverse events in controlled clinical studies occurring in <1.5% of patients.[7,12,13]

| Contrast Agent* | No. of Patients | Headache (%) | Nausea (%) | Taste Perversion (%) | Rash (%) |
|---|---|---|---|---|---|
| **ProHance[7]** | **1,251** | **<1.0** | **1.4** | **1.4** | **<1.0** |
| Dotarem®[9] | 2,867 | 0.4 | 0.6 | <0.2 | 0.2 |
| Gadavist®[10] | 6,809 | 1.5 | 1.1 | 0.4 | 0.3 |

**ProHance:**
**The only agent still FDA approved for triple dosing[7]**

**Safe for use in children (>2 years of age) and those with renal insufficiency[7]**

- Indicated for use in MRI in children (>2 years of age) to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine, and associated tissue

*Clinical trials are conducted under widely varying conditions, and thus 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.

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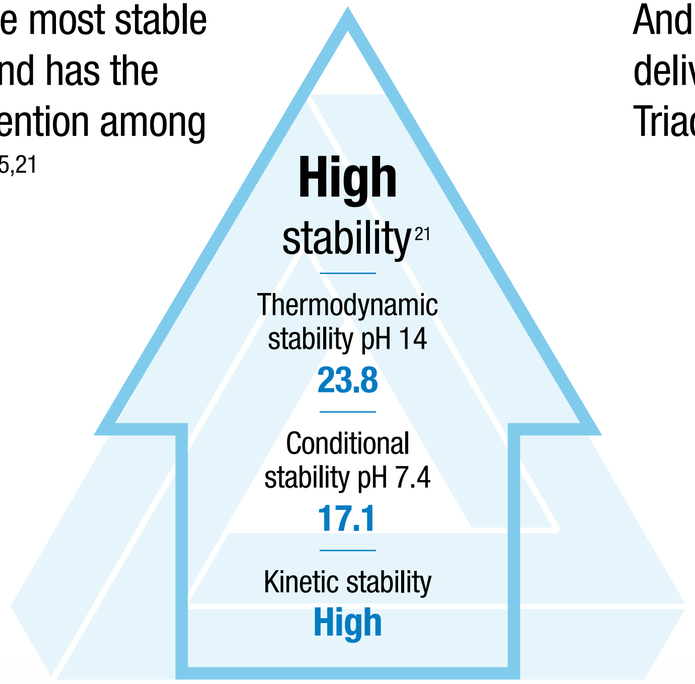
# High-Stability Macrocyclic GBCA

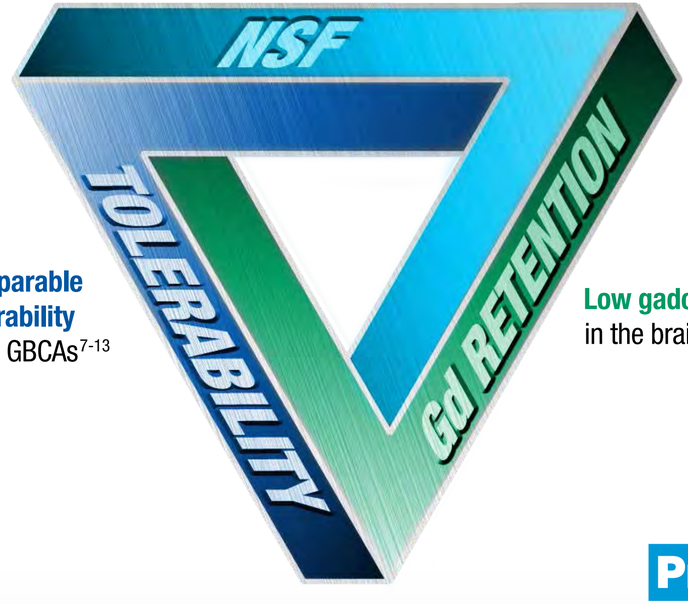
## Not all macrocyclic GBCAs are created equal

ProHance is one of the most stable macrocyclic GBCAs and has the lowest gadolinum retention among macrocyclic agents.[2-5,21]




And only ProHance delivers the Triad of Benefits:

**No medically confirmed unconfounded cases of NSF**
in more than 28 million doses worldwide[6,14]




**Comparable tolerability**
to other GBCAs[7-13]

**Low gadolinium retention**
in the brain and kidneys[2-5,*]

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- 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 and
- Magnetic resonance angiography (MRA) to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease

**Indications and Usage for ProHance® (Gadoteridol) Injection, 279.3 mg/mL:**

CENTRAL NERVOUS SYSTEM
ProHance (Gadoteridol) Injection, 279.3 mg/mL 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 (Gadoteridol) Injection, 279.3 mg/mL is indicated for use in MRI in adults to visualize lesions in the head and neck.

**IMPORTANT SAFETY INFORMATION for MultiHance and ProHance:**

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- For patients at highest risk for NSF, do not exceed the recommended MultiHance/ProHance dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration. (see ***WARNINGS***)

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Anaphylactic and anaphylactoid reactions have been reported, involving cardiovascular, respiratory, and/or cutaneous manifestations ranging from mild to severe. The possibility of a reaction should always be considered, especially in those patients with a history of a known clinical hypersensitivity or a history of asthma or other allergic disorders. Trace amounts of gadolinium may remain for months or years in the body organs including bone (highest concentration), brain, liver, spleen, kidneys and skin. Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of retention in skin and other organs have been established in patients with impaired renal function. Minimize repetitive GBCA imaging studies, particularly close spaced studies when possible.

**ProHance (Gadoteridol) Injection, 279.3 mg/mL**
As with all paramagnetic agents, caution should be exercised in patients with deoxygenated sickle erythrocytes and renal insufficiency with or without hepatic impairment. The possibility of a reaction, including serious, life threatening, or fatal, anaphylactic or cardiovascular reactions, or other idiosyncratic 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 disorders. Trace amounts of gadolinium may remain for months or years in the body organs including bone (highest concentration), brain, liver, spleen, kidneys and skin. Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of retention in skin and other organs have been established in patients with impaired renal function. Minimize repetitive GBCA imaging studies, particularly close spaced studies when possible.

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MultiHance® (gadobenate dimeglumine) is manufactured for Bracco Diagnostics Inc. by BIPSO GmbH – 78224 Singen (Germany) and by Patheon Italia S.p.A., Ferentino, Italy.

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