ProHance 279.3mg/ml,
solution for injection

Package Insert

Exposure to Gadolinium - based contrast agents (GBCAs) increases the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with:
- acute or chronic severe renal insufficiency (glomerular filtration rate <30mL/min/1.73m2), or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the preoperative liver transplantation period.
• NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.
• Avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).
• Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
• When administering GBCAs, do not exceed the dose recommended in product labeling. Allow sufficient time for elimination of the GBCA prior to any readministration.

a) Brand or Product Name
ProHance 279.3mg/ml, solution for injection

b) Name and Strength of Active Substance(s)
1 mL of solution for injection contains 279.3 mg of gadoteridol (equivalent to 0.5 mmol/mL of gadoteridol).
Excipient with known effect: this medicinal product contains less than 1 mmol (23 mg) of sodium per vial, that is to say essentially "sodium-free".
List of excipients:
Calcium calteridol.Trometamol.
Hydrochloric acid or sodium hydroxide (for pH adjustment).
Water for injection

c) Product Description
Solution for injection (IV).
Clear, colourless to yellowish solution, without visible particles.
pH of the solution is between 6.5 to 8.0 and its osmolality is 630 mOsmol/kg. viscosity at 20°C: 2 mPa-S

d) Pharmacodynamics/ PharmacokineticsPharmacodynamic properties
Pharmacotherapeutic group: Contrast media, magnetic resonance imaging contrast media, ATC code: V08CA04.
Gadoteridol is a paramagnetic, non-ionic contrast product used in magnetic resonance imaging. Gadoteridol, when placed in a magnetic field, reduces the longitudinal relaxation time in targeted regions. At the recommended doses, this effect is particularly sensitive in T1 relaxation time weightedsequences.
Central Nervous System
ProHance was evaluated in three clinical studies in a total of 562 adults (298 men, 264 women) with age ranging from 18 to 87 years who had an indication for MRI of intracranial or spinal pathology. All patients received a single 0.1 mmol/kg intravenous dose of ProHance. Contrast enhancement was noted in all studies for at least 70% of patients with brain pathology and for at least 57% with spinalpathology. Additional information by contrast injection on both brain and spinal tumors was gainedfor 43% to 76% of the patients. Diagnoses were changed from pre-contrast to post-contrast imagesin 54%-84% of the cases for brain disease and in 33% to 76% for spine pathology.
One study was conducted to assess the efficacy of high-dose (0.3 mmol/kg given as a cumulative two

injections of 0.1 mmol/kg + 0.2 mmol/kg) ProHance in MR imaging of brain metastases in 67 patients. Both blinded and unblinded readings of the images confirmed a significantly higher number of metastatic lesions detected at 0.3 mmol/kg dose compared to 0.1 mmol/kg dose. Additional diagnostic information in terms of number of lesions, improved lesion visualization and better definition of lesion borders by the 0.3 mmol/kg was obtained in 64% to 78% of the cases dependingon the readers.
ProHance was also evaluated in a clinical trial of 103 children (54 boys and 49 girls) with an age range from 2 to 20 years who had an indication for a brain or spine MRI. ProHance was given in one single 0.1 mmol/kg dose. MRI enhancement was noted in approximately 60% of the scans and additional diagnostic information were obtained in 30-95% of the scans.

Head & Neck

ProHance was evaluated at a dose of 0.10 mmol/kg in two blinded read trials in a total of 133 adults(74 men, 59 women) with an age range from 19 to 76 years who had an indication for head and neck extracranial or extraspinal MRI. In approximately 75-82% of the scans contrast enhancement was noted. In 45-48% of the scans contrast injection provided additional diagnostic information.

Musculoskeletal and soft tissue pathology

A study was conducted on 174 patients (107 men, 66 women, 1 missing) with an age range from 11 to 83 years suspected of having musculoskeletal or soft tissue pathology (primary or secondary tumours and non-acute inflammatory disease). For the analysis of imaging efficacy, 137 patients wereimaged at 0.10 mmol/kg and 56 patients imaged at 0.30 mmol/kg (mostly primary or secondary tumours, rheumatoid arthritis and non-acute inflammatory disease). The results indicate that static and dynamic imaging at a dose of 0.10 or 0.30 mmol/kg provides additional diagnostic information in a significant number of patients compared to pre-dose images ranging from between 16% to 82%for static imaging and 11% to 95% for dynamic imaging (all readers).

Liver

ProHance was evaluated in one study with 201 adult patients (102 men and 91 women) with an agerange from 18 to 91 years highly suspected of having focal liver pathology. Blinded reader assessments indicated post-dose images providing additional diagnostic information, in 31% to 68%of the cases when compared with predose images. Diagnoses were changed by contrast injection for35% to 78% of the cases.

Breast

ProHance was assessed in two clinical studies in 327 female patients with an age range between 20 and 79 years and suspected breast pathology. Blinded reader assessments of images at 0.10 mmol/kg(111 patients), 0.20 mmol/kg (109 patients), and 0.30 mmol/kg (107 patients) show that ProHance at all doses delivered contrast enhancement of breast pathology in 70% to 92% of the cases and provided additional information gained in 57% to 100% of the patients (across all blinded readers from the 2 studies).

Pharmacokinetic properties

Modelling of the human pharmacokinetics was well described using a biexponential decay model. Gadoteridol ion is rapidly cleared from plasma and is eliminated in urine.

A population pharmacokinetic analysis was performed on systemic drug concentration-time using data from 79 subjects (51 adult volunteers including 24 with impaired renal function and 28 paediatric patients) aged 5 to 73 years following intravenous administration of gadoteridol. The simulation model showed that kinetics of gadolinium down to the age of 2 years could be describedby a two-compartment model with standard allometric coefficients and a covariate effect of creatinine clearance (reflecting glomerular filtration rate) on gadolinium clearance. The pharmacokinetic parameter values (referenced to adult body weight) were consistent with the physiology presumed to underlie ProHance distribution and elimination.

Distribution

The absolute distribution volume (L) was lower for younger subjects, but this effect was largely compensated for by normalizing volume per kg of body weight. Unlike normalized clearance, normalized distribution volume did not change greatly with age, with pediatric values being within 15% of non-renally impaired adult values. The plasma distribution volume values for the non-renallyimpaired adults of the combined data set was 205 ± 25 mL/kg. The distribution (alpha) half-life for the non-renally

impaired adults was 0.235 ± 0.119 h. Younger subjects were associated with lower distribution half-lives, with 2-6 year old and 6 to 12 years old being 60% and 78%, respectively, of non-renally impaired adult values. The beta (elimination) half-life for the non-renally impaired adultswas 2.00 ± 0.437 h. Younger subjects were associated with lower elimination half-lives, with 2-6 yearold and 6-12 year old being 66% of adult values.

Elimination

The plasma clearance values for the non-renally impaired adults was 1.38 ± 0.03 mL/min/kg. Younger subjects were associated with higher normalized clearance values, with 2-6 year olds and 6-12 yearsolds being 169% and 166%, respectively, of adult non-renally impaired values. A simulation approach was used to assess the consequences of using a mmol per kg dose regimen in younger children andneonates. There was a tendency for the younger age groups to have concentrations lower than the median value for adults. The alpha half-lives were found to decrease progressively with age, whilethe beta half-lives were lowest for subjects near 2 years old. The lowest alpha half-life was 25.5%(male) and 26.1% (female) of non-renally impaired adult values for the 0 to 1 month subjects. The lowest beta (elimination) half-life was 78.0 and 78.5% of non-renally impaired adult values for 12 to24 months old subjects. Using weight based dosing for ProHance in pediatric subjects under 2 years old gives similar, or lower than, AUC and C_{max} values to those reported for adults and children olderthan 2 years of age, supporting that no dose adjustment is necessary for this pediatric population. The average cumulative urinary excretion was reduced as a function of renal impairment andaccounted for 85.8%± 13.4 of the injected dose 7 days after dosing compared to that of the normalsubjects (94.4 ± 4.8% of the injected dose within 24 hours).

During hemodialysis the clearance rate of gadoteridol was comparable to those of creatinine and blood urea nitrogen (BUN). Approximately 72% of the injected dose was cleared from the blood after the first dialysis session, 91% after the second and 98% after the third.

Preclinical safety data

Single-dose studies in mice and rats showed that the maximum non-lethal dose was 7 mmol/kg and10 mmol/kg respectively (more than 20 and 30 times the maximum clinical dose of 0,3 mmol/kg, respectively).

Some vacuolative changes in the renal cortical epithelium, reversible upon cessation of treatment,were noted both in rats and dogs in the 28-day studies in doses greater than 0.3 mmol/kg and 1 mmol/kg respectively.

ProHance did not show any genotoxic - effects in a series of *in vitro* and *in vivo* tests.

Since ProHance is for single dose administration and is devoid of any genotoxic potential, no carcinogenicity studies have been conducted.

Fertility study was conducted in Sprague Dawley rats using ProHance injection at maximal IV dose levels of 6 mmol/kg/day. No effect on reproductive function was demonstrated after ProHance administration.

ProHance exerted no untoward effects on embryonic or foetal development, at daily doses in rabbits at least 60 times and in rats at least 100 times the recommended human dose of 0.1 mmol/kg.

No potential to cause local irritation after intra-arterial administration has been demonstrated.

e) Indication

This medicinal product is for diagnostic use only.

Using Magnetic Resonance Imaging (MRI), ProHance provides contrast enhancement of the brain, spine and surrounding tissues resulting in improved visualization (compared with unenhanced MRI) of lesions with abnormal vascularity or those thought to cause a disruption of the normal blood-brain barrier. ProHance can also be used for whole body MRI including the head, neck, liver, breast, muscoloskeletal system and soft tissue pathologies.

ProHance should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

f) Recommended Dosage

Method of administration:

ProHance is used by intravenous route and as a single dose.

-In order to guarantee the injection of the prescribed dose, the injection should be followed by a bolus of 5 mL of solution of sodium chloride 9 g/L.

-The imaging procedure should be performed within the hour following injection.

Make sure that the injection is strictly intravenous in case of –extravasation, local intolerance reactions may observed, requiring the usual local care.

Do not use by intrathecal route.

Posology

The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section.

Adults

The recommended dose of ProHance for imaging most brain and spinal pathologies is 0.1 mmol/kg (0.2 ml/kg). However, doses of 0.3 mmol/kg (0.6 ml/kg) have been shown to be useful in patients suspected of having cerebral metastases or other poorly enhancing lesions. The recommended dose for whole body MRI is 0.1 mmol/kg (0.2 ml/kg).

Paediatric population

Children of any age (from term neonates)

The recommended dose of ProHance for brain imaging and spine pathologies is 0.1 mmol/kg (0.2 ml/kg). ProHance has been used in only a limited number of children aged between birth and 2 years. If an MRI procedure must be performed in this group, particular caution should be exercised. The safety and efficacy of doses higher than 0.1 mmol/kg (0.2 ml/kg) and sequential or repeat procedures have not been established.

Special Populations

Impaired renal function

ProHance should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73m2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see section i). If it is necessary to use ProHance, the dose should not exceed 0.1 mmol/kg (0.2 ml/kg) body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, ProHance injections should not be repeated unless the interval between injections is at least 7 days.

Neonates up to 4 weeks of age and infants up to 1 year of age

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, ProHance should only be used in these patients after careful consideration at a dose not exceeding 0.1 mmol/kg (0.2 ml/kg) body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, ProHance injections should not be repeated unless the interval between injections is at least 7 days. Use for whole body MRI is not recommended in children less than 18 years of age

Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients.

g) Route of Administration

Intravenous IV.

h) Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients, see section b).

i) Warnings and Precautions

- Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA.
- For patients receiving haemodialysis, healthcare professionals may consider prompt haemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if haemodialysis prevents NSF.
- Determine the renal function of patients by obtaining a medical history of conducting laboratory tests that measure renal function prior to using GBCA.
- The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.
- Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs

Warnings

- All MRI contrast products can cause minor or major hypersensitivity reactions, which can be life-threatening. They can be immediate (less than 60 minutes) or delayed (up to 7 days). Anaphylactic reactions are immediate and can lead to death. They are independent of the dose, may occur upon the first administration of the product, and are often unforeseeable.
- The risk of an anaphylactic reaction makes it necessary to have immediate access to the resources necessary for emergency life support (including an emergency trolley).
- In case of reaction occurrence, patients should benefit of an immediate immunologic check and a specialised allergologic check after at least 4 weeks.
- Patients having already presented with a reaction during a previous administration of an MRI contrast product containing gadolinium, having allergy history, reaction to medicines or hypersensitivity troubles, have an increased risk of another reaction in case of re-administration of the same product,or possibly another product, and are therefore considered to be at risk subjects.
- Anaphylactic shocks with ProHance have been very rarely reported.
- Gadoteridol must not be used intrathecally. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use.

Precautions for use

Hypersensitivity to MRI contrast products

Before the procedure:

- Identify at risk subjects using a precise interview on previous medical history.
- Corticosteroids and H1 antihistamines have been proposed as premedication in patients with the highest risk of an intolerance reaction (known intolerance to a contrast product). However,they do not prevent the occurrence of serious or fatal anaphylactic shock.

During the duration of the procedure, it is necessary to provide:

- medical monitoring,
- maintenance of a venous access.

After the procedure:

- After administration of a contrast product, the patient should remain in observation at least 30 minutes, because the majority of serious adverse effects occur within this interval.
- The patient should be informed of the possibility of delayed reactions (up to 7 days) (seesection l).

Impaired renal function

Prior to administration of ProHance, it is recommended that at risk patients and elderly are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (creatinine clearance or GFR < 30 ml/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with ProHance, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefitassessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after ProHance administration may be useful at removing ProHance from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment ofNSF in patients not already undergoing haemodialysis.

Neonates and infants

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, ProHance should only be used in these patients after careful consideration.

Elderly

As the renal clearance of gadoteridol may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Central nervous system disorders

In patients suffering from epilepsy or brain lesions the likelihood of convulsions during the examination is increased. Medical monitoring of these patients is necessary during the procedure. The equipment and medicinal products needed for the quick treatment of possible convulsions should be available.

Excipients with noteworthy effects

This medicinal product contains sodium. This medicinal product contains less than 1 mmol (23 mg) of sodium per vial, that is to say essentially "sodium-free".

j) Interactions with Other Medicaments

There are no known drug interactions with ProHance

k) Statement on usage during pregnancy and lactation

Pregnancy

Data on the use of gadolinium-based contrast agents including gadoteridol in pregnant women is limited. Gadolinium can cross the placenta. It is unknown whether exposure to gadolinium is associated with adverse effects in the foetus. Studies performed in animals have not shown any noxious effects, direct or indirect on reproduction. ProHance should not be used during pregnancy; only examinations absolutely necessary should be performed during pregnancy, when the probable benefit clearly outweighs the risk for the mother and the foetus.

Breast-feeding

Gadolinium containing contrast agents are excreted into breast milk in very small amounts. At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing breast feeding or discontinuing ProHance for a period of 24 hours after administration, should be at the discretion of the doctor and lactating mother.

Fertility

No effect on fertility was observed during fertility study.

l) Adverse Effects/ Undesirable Effects

In clinical studies on 2827 patients, 6.3% of patients presented with an undesirable effect related to the administration of ProHance.

Undesirable effects related to the use of ProHance are generally mild to moderate in intensity, and transitory.

The undesirable effects most commonly encountered upon administration of ProHance since its marketing are nausea.

Hypersensitivity reactions most commonly observed effects are cutaneous reactions, which may be localised, extended or generalised. These reactions usually occur immediately (during the injection or within the hour following the start of the injection) or sometimes delayed (one hour to a few days after the injection).

Immediate skin reactions may involve one or more types of skin, respiratory and/or cardiovascular reactions, occurring concomitantly or successively. Each of them can be the first sign of a state of shock, which very rarely evolve to death.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with ProHance in patients co-administered other gadolinium-containing contrast agents (see section i).

The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100),Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data)

System Organ Class	**Adverse Drug Reactions** **Frequency Category**
Immune system disorders	Rare: anaphylactic reaction*
Psychiatric disorders	Rare: anxiety
Nervous system disorders	Uncommon: headaches, dizzy feeling, paraesthesia, dysgeusia, Rare: convulsion, abnormal coordination, mental impairment Not known: coma, vasovagal reaction**, loss of consciousness
Eye disorders	Uncommon: increased lachrymal secretion
Ear and labyrinth disorders	Rare: tinnitus
Cardiac disorders	Uncommon: increased cardiac rhythm Rare: nodal rhythm troubles Not known: cardiac arrest
Vascular disorders	Uncommon: hypotension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Rare: laryngospasm, dyspnoea, cough, rhinitis, apnea, stridor Not known: respiratory arrest, pulmonary oedema

Gastrointestinal disorders	Common: nausea Uncommon: vomiting, dry mouth Rare: diarrhoea, abdominal pain, tongue oedema, oral pruritus, gingivitis
Skin and subcutaneous tissue disorders	Uncommon: pruritis, urticaria, rash Rare: face oedema Not known: nephrogenic systemic fibrosis, angioedema
Musculoskeletal and connective tissue disorders	Rare: muscular stiffness
Renal and urinary disorders	Not known: acute renal failure***
General disorders and administration site conditions	Uncommon: pain at the injection site, reaction at the injection site (including due to product extravasation), asthenia Rare: fever, thoracic pain

* Anaphylactic reactions
As with other gadolinium chelates, there have been reports of anaphylactic/ hypersensitivity reactions with ProHance. These reactions manifested with various degrees of severity, including anaphylactic shock or death. They involved one or more body systems, mostly respiratory, cardiovascular and/or mucocutaneous systems. Commonly reported symptoms include throat tightness, throat irritation, dyspnoea, chest discomfort, feeling hot, dysphagia, burning sensation, oedema in pharynx or larynx, and hypotension.

**Vasovagal reactions
Vasovagal reactions, rarely leading to vasovagal syncope have been reported during or immediately after ProHance administration. The condition is often related to emotional distress or painful/unpleasant stimuli (e.g. needle puncture for IV placement). Symptoms commonly experiencedinclude nausea, dizziness and diaphoresis.
In severe cases possibly leading to syncope, patients are usually pale and diaphoretic with altered state of consciousness and bradycardia. In addition, patients could frequently experience apprehension, restlessness, felt faint and salivary hypersecretion. Proper recognition of this reaction and differential diagnosis with hypersensitivity reaction is vital in order to apply the appropriate treatment measures to revert the vagal stimulation.

*** Acute renal failure
Cases of acute renal failure have been reported in patients with pre-existing severe renal impairment.

Paediatric population
The frequency, nature and severity of adverse reactions in children are similar to those observed in adults. However, data come from a single paediatric study having included 103 children between 6 months and 20 years.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

m) Overdose and Treatment
No overdose has been reported.

In case of a very high dose, water and electrolyte loss should be compensated by appropriate rehydration. Renal function should be monitored for at least three days.

ProHance can be eliminated from the body by haemodialysis. However, it has not been demonstratedthat haemodialysis is appropriate in the prevention of nephrogenic systemic fibrosis (NSF).

n) Incompatibilities (For injections only)

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

o) Storage Conditions

Store below 30°C in the original package protected from light.

Shelf life

3 years.

After opening, the product must be used immediately

Special precautions for disposal and other handling

The peel-off tracking label on the vial should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. In case of electronic patient record, the name of the product, the batch number and the dose should be recorded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Used vials must be destroyed according to standard procedures applicable to imaging contrast media.

p) Dosage forms and packaging available

Vials of 10, 15 and 20 mL (type I glass with a grey butyl stopper and an aluminium cap. Box containing1 vial (single dose).

Not all pack sizes may be marketed.

q) Name and address of manufacturer/ product registration holder

Name and address of manufacturer for Bracco Suisse SA

Bracco Imaging S.P.A.
Bioindustry Park
Via Ribes 5
10010 Colleretto Giacosa (TO)
Italy

Product registration holder

DCH Auriga (Malaysia) Sdn. Bhd.
Lot 6, Persiaran Perusahaan, Seksyen 23,
403000 Shah Alam, Selangor Darul Ehsan,
Malaysia.

Product owner

Bracco Suisse SA
Via Ponteggia, 23
CH - 6814, Cadempino
Switzerland

r) Date of revision

June 2025