SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ProHance 279.3 mg/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Gadoteridol 279.3mg per ml (0.5M)

3 PHARMACEUTICAL FORM

Sterile solution for intravenous injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

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/1.73m^2) 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 4.4). 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 (see section 4.4).

Method of administration

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 after injecting ProHance.

Caution during injection of any contrast media is necessary to avoid extravasation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to other gadolinium-based contrast.

4.4 Special warnings and precautions for use

Patients with a history of allergy, drug reactions, or other hypersensitivity-like disorders should be closely observed during the procedure and the contrast medium administration, as well as for the time the physician deems useful given the patient condition.
As with other gadolinium chelates, there have been reports of anaphylactic/anaphylactoid/ hypersensitivity reactions with gadoteridol 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.
Anaphylactic shock has been very rarely reported with the use of gadoteridol.

Appropriate drugs and instruments for emergency measures must be readily available.

In patients suffering from epilepsy or brain lesions the likelihood of convulsions during the examination may be increased. Precautions are necessary when examining these patients (e.g. monitoring of the patient) and the equipment and medicinal products needed for the rapid treatment of possible convulsions should be available.

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.

Transitory changes in serum iron (within normal range in the majority of cases) have been observed in some patients after administration of ProHance and these changes were shown not to be clinically significant.
Caution during injection of any contrast media is necessary to avoid extravasation.

Since Gadoteridol is renally cleared from the body, caution should be exercised in patients with severely impaired renal function.

Impaired renal function

Prior to administration of ProHance, it is recommended that all patients 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 (GFR < 30 ml/min/1.73m2). 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/benefit assessment 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 of NSF 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.

4.5 Interaction with other medicinal products and other forms of interaction

There are no known drug interactions with Gadoteridol. No clinically significant changes or trends in laboratory tests were seen in clinical trials with ProHance®.

4.6 Fertility, pregnancy and lactation

Fertility
There are no fertility data.

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. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). ProHance should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteridol.

Lactation
Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). 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 or discontinuing breast feeding for a period of 24 hours after

administration of ProHance, should be at the discretion of the doctor and lactating mother.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacokinetic and pharmacodynamic profiles, no or negligible influence is expected with the use of ProHance on the ability to drive or use machines.

4.8 Undesirable effects

The accepted safety considerations and procedures that are required for Magnetic Resonance Imaging are applicable when ProHance is used for contrast enhancement.

The following adverse reactions have been reported with ProHance. adverse reactions from clinical trials have been included with an indication of the frequency. Adverse reactions from spontaneous reporting are included with the frequency “not known”. There were no adverse reactions with an incidence greater than 2%.

System Organ Class	Adverse Reactions			
	Common (≥1/100 - <1/10)	Uncommon (≥1/1000 - <1/100)	Rare (≥1/10,000 - <1/1000)	Not known (cannot be estimated from the available data)
Immune system disorders			Anaphylactic/anaphylactoid reactions***	
Psychiatric disorders			anxiety	
Nervous system disorders		headache, paraesthesia, dizziness, taste disturbance	mental impairment, abnormal coordination, convulsion	loss of consciousness, coma, vasovagal reactions*
Eye disorders		increased lacrimation		
Ear and labyrinth disorders			tinnitus	
Cardiac disorders			nodal arrhythmia	cardiac arrest
Vascular disorders		flushing, hypotension		
Respiratory, thoracic and mediastinal disorders			laryngospasm, dyspnoea, rhinitis, cough, apnea, wheezing	respiratory arrest , pulmonary oedema
Gastrointestinal disorders	nausea	dry mouth, vomiting	abdominal pain, tongue oedema, oral pruritus, gingivitis, loose stools	
Skin and subcutaneous tissue disorders		pruritus, rash, urticaria	oedema face	
Musculoskeletal and connective tissue disorders			musculoskeletal stiffness	
Renal and urinary system				acute renal failure**
General disorders and administration site conditions		injection site pain, injection site reaction ****, asthenia	chest pain, pyrexia	
Investigations		heart rate increased		

Description of selected adverse reactions

*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 experienced include 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, faintness and salivary hypersecretion. Proper recognition of this reaction and differential diagnosis with hypersensitivity/anaphylactoid 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.

***Anaphylactic/anaphylactoid reactions
As with other gadolinium chelates, there have been reports of anaphylactic/anaphylactoid/ hypersensitivity reactions with gadoteridol. 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.

**** Injection site reactions are mainly characterised by local pain, erythema or swelling, and in some cases they are a consequence of an extravasation.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with ProHance, most of which were in patients co-administered other gadolinium-containing contrast agents (see section 4.4).

Paediatric Patients

The ProHance safety profile is similar in children and adults.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There have been no cases of overdose reported to date, consequently, neither signs nor symptoms of overdosage have been identified. In the event of overdosage occurring, the patient should be observed and treated symptomatically.

ProHance can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: magnetic resonance imaging contrast media, ATC code: V08CA04

Mechanism of action Gadoteridol is a non-ionic paramagnetic contrast medium for Magnetic Resonance Imaging.

When placed in a magnetic field, gadoteridol decreases T1 relaxation times in targeted areas. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

Pharmacodynamic effects

However, disruption of the blood-brain barrier or normal vascularity allows penetration of gadoteridol into lesions such as neoplasms, abscesses, and subacute infarcts.

5.2 Pharmacokinetic properties

Distribution

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 ± 10.04 hours and 1.57 ± 10.08 hours, respectively.

Elimination

Gadoteridol 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 1 kg) is equal to that of extra cellular water, and clearance is similar to that of substances which are subject to glomerular filtration.

No serum protein binding was detected in rats.

5.3 Preclinical safety data

Preclinical data indicate no additional risks for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity. Carcinogenicity studies have not been conducted.

Reproduction toxicity studies gave no indication of teratogenic potential. Rats and rabbits that received gadoteridol for 12-13 days during gestation showed an increase in post-implantation loss / abortion at doses 20-33 times the maximum human dose of 0.3mmol/kg/day. The offspring of rats treated at this dose also showed an increased spontaneous motor activity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calteridol Calcium

Tromethamine

Hydrochloric Acid

Sodium Hydroxide

Water for Injections

6.2 Incompatibilities

ProHance® should not be admixed with any other drug.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at room temperature (15-30°C.), protect from light.

Frozen syringes should be discarded.

6.5 Nature and contents of container

Syringes: Type I glass syringes with rubber stoppers and polypropylene plunger rods containing 5,10, 15 or 17 ml.

6.6 Special precautions for disposal

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

b. Holding syringe erect, aseptically remove the rubber cap from the tip of the syringe and attach either a sterile, disposable needle or tubing with a compatible luer lock using a push-twist action.

c. Hold the syringe erect and push plunger forward until all the air is evacuated and fluid either appears at the tip of the needle or the tubing is filled. Following the usual aspiration procedure, complete the injection. To ensure complete delivery of the contrast medium, the injection should be followed by a normal saline flush.

d. Properly dispose of the syringe and any other material used.

The peel-off tracking label on the syringes should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bracco UK Ltd, Magdalen Centre
The Oxford Science Park, Oxford, OX4 4GA, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 18920/0038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 February 1997 / 26 March 2003

10 DATE OF REVISION OF THE TEXT

01/08/2024