Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ProHance, 279.3 mg/ml, solution for injection, 20 ml vial

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Gadoteridol 279.3 mg per ml (0.5 mmol), 5586 mg per 20 ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear colourless to pale yellow sterile solution for intravenous use.

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 visualisation (compared with unenhanced MRI) of lesions with abnormal vascularity or those thought to cause a disruption of the normal blood-brain barrier.

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, in patients suspected of having cerebral metastases or other poorly enhancing lesions 0.3 mmol/kg (0.6 ml/kg) is recommended. To ensure complete injection of the contrast medium, the injection should be followed by a 5ml 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.

Paediatric population

Children
The safety and effectiveness of ProHance in children 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

0.1mmol/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.

Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

4.3 Contraindications

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

ProHance is contraindicated in children under 18 months of age.

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 Necessary medication and equipment should be available in case of severe reactions should they occur.
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.
If in the clinical judgement of the radiologist, an additional injection of ProHance is warranted to extend an enhanced examination, and additional dose of 0.1 mmol/kg may be administered at approximately 30 minutes after the first injection. In the event that repeat examinations are indicated, a period of approximately 6 hours should be observed in order to allow for normal clearance of ProHance.
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/1.73m^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/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.

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-gadoteridol on the ability to drive or use machines.

4.8 Undesirable effects

The following adverse reactions have been reported with gadoteridol. 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 clinical trial 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			laryngospasm, dyspnoea, rhinitis, cough, apnea, wheezing	Respiratory arrest ,

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 clinical trial data)
mediastinal disorders				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 (eventually due to extravasation of the contrast)" ,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 gadoteridol 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.

Nephrogenic systemic fibrosis

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).

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There have been no cases of overdoses reported to date, consequently, neither signs nor symptoms of overdosage have been identified. In clinical studies using doses up to 0.3 mmol/kg, no clinical consequences relating to increasing dose have been observed. 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

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.

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

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.

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/kg) is equal to that of extracellular 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

Toxicity
Single-dose studies in mice and rats showed that the maximum non-lethal dose was 7 mmol/kg and 10 mmol/kg respectively (more than 20 and 30 times the maximum clinical dose, 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.

Mutagenesis
ProHance did not show any mutagenic effects in a series of in vitro and in vivo tests. No genetic, chromosomal, nor DNA damage was shown even in the presence of metabolic activation.

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

Reproduction

No effect on reproductive function was demonstrated after ProHance administration.

Teratogenicity
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 irritation after intraarterial administration has been demonstrated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calteridol Calcium
Tromethamine
Hydrochloric Acid (for pH adjustment)
Sodium Hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

ProHance should not be admixed with any other drug.

6.3 Shelf life

Unopened: 3 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton. Do not refrigerate or freeze.

6.5 Nature and contents of container

Type I glass vials with:
- grey latex-free butyl rubber stoppers with fluororesin coating and aluminium seal, containing 20 ml.
- grey latex-free bromobutyl or clorobutyl rubber stoppers and aluminium seal, containing 20 ml.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.
Discard any unused contents.

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.

7 MARKETING AUTHORISATION HOLDER

Bracco International B.V.
Strawinskylaan 3051
1077 ZX Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0788/001/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd February 1993
Date of last renewal: 23rd February 2008

10 DATE OF REVISION OF THE TEXT

August 2024