

Revised: September 2011 (15th version)

Standard Commodity Classification No. of Japan
87729

- Nonionic contrast medium for MRI -

**ProHance**<sup>®</sup> for Intravenous Injection 5mL  
**ProHance**<sup>®</sup> for Intravenous Injection 10mL  
**ProHance**<sup>®</sup> for Intravenous Injection 15mL  
**ProHance**<sup>®</sup> for Intravenous Injection 20mL  
**ProHance**<sup>®</sup> for Intravenous Injection Syringe 13mL  
**ProHance**<sup>®</sup> for Intravenous Injection Syringe 17mL

&lt;Gadoteridol injections&gt;

Prescription drug

	For i.v. Injection 5mL	For i.v. Injection 10mL	For i.v. Injection 15mL
Approval No.	22100AMX00462000	22100AMX00499000	22100AMX00500000
Date of listing in the NHI reimbursement price	Sep 2009		
Date of initial marketing in Japan	Jul 1994	Jan 1997	Jul 1994
Date of latest reexamination	Mar 2004		
Date of latest approval of indications	Aug 1999		

	For i.v. Injection 20mL	For i.v. Injection Syringe 13mL	For i.v. Injection Syringe 17mL
Approval No.	22100AMX00461000	22100AMX00463000	22100AMX00464000
Date of listing in the NHI reimbursement price	Sep 2009		
Date of initial marketing in Japan	Jul 1994	Jul 2002	
Date of latest reexamination	Mar 2004	---	
Date of latest approval of indications	Aug 1999	---	

Storage
PROHANCE should be stored at room temperature.

Expiration date
PROHANCE should be used before the expiration date indicated on the package or label.

Caution: Use only as directed by a physician.

**WARNINGS**

1. Never inject PROHANCE into the brain and spinal canal, because such intracerebral and intramedullary administration may cause serious adverse reactions.
2. It has been reported that patients with serious renal function disorders have an increased risk of nephrogenic systemic fibrosis associated with the use of gadolinium-based contrast media. Patients with renal function disorders or possible renal impairment should be carefully observed. [See “Careful Administration” and “Important Precautions” sections]

**CONTRAINDICATIONS (PROHANCE is contraindicated in the following patients.)**

1. Patients who have previously had serious adverse reactions to PROHANCE.
2. Patients with a history of hypersensitivity to any ingredients of PROHANCE or other contrast media containing gadolinium-compounds.

**RELATIVE CONTRAINDICATIONS (As a general rule, PROHANCE is contraindicated in the following patients. If the use of PROHANCE is considered essential, it should be administered with care.)**

1. Patients whose general condition is very poor
2. Patients with bronchial asthma [Anaphylactoid reaction may occur.]
3. Patients with serious renal function disorders [Since

PROHANCE is excreted mainly through the kidneys, excretion may be delayed and renal function may be impaired.]

4. Patients who require an additional dose when there has been an adverse reaction to the first dose.

**DESCRIPTION**

Each vial and syringe contains following ingredients.

Component		Content per vial				Content per syringe	
		5mL	10mL	15mL	20mL	13mL	17mL
Active ingredient	Gadoteridol	1396.5 mg	2793.0 mg	4189.5 mg	5586.0 mg	3630.90 mg	4748.10 mg
	Calteridol calcium	1.15mg	2.30mg	3.45mg	4.60mg	2.99mg	3.91mg
Inactive ingredients	Trometamol	6.05mg	12.10mg	18.15mg	24.20mg	15.73mg	20.57mg
	Hydrochloric acid	q.s.					
	Sodium hydroxide	q.s.					
Product description		PROHANCE is a colorless, clear liquid.					
pH		6.5-8.0					
Osmotic pressure ratio		about 2 (ratio relative to isotonic sodium chloride solution)					
Viscosity (at 37°C)		1.3 mPa·s					

**INDICATIONS**

The following examinations by magnetic resonance imaging and computer tomography scanning  
 Myelography, encephalography, and radiographic MRI examination of the trunk and limbs

## DOSAGE AND ADMINISTRATION

The usual adult dosage for intravenous use is 0.2 mL/kg of PROHANCE.

In the case of renal examinations, the dosage for intravenous use is 0.1 mL/kg of PROHANCE.

For patients suspected of having a metastatic brain tumor, if no tumor is detected or the radiographic efficacy is insufficient when a tumor has been detected after a 0.2 mL/kg dose, an additional 0.2 mL/kg dose may be administered within 30 min of the first dose.

## PRECAUTIONS

### 1. Careful Administration (PROHANCE should be administered with care in the following patients.)

- (1) Patients with a personal predisposition to allergic reactions, such as allergic rhinitis, rash or urticaria
- (2) Patients with a familial predisposition to allergic reactions, such as allergic rhinitis, rash or urticaria
- (3) Patients with a history of drug hypersensitivity
- (4) Patients with convulsions or epilepsy (including those with a history of such disorders)  
[Convulsions may occur.]
- (5) Patients with a renal function disorder or potentially compromised renal function
- (6) Elderly patients  
[See "Use in the Elderly" section.]
- (7) Children  
[See "Pediatric Use" section.]

### 2. Important Precautions

- (1) Serious adverse reactions such as **shock or anaphylactoid reactions** may occur. When PROHANCE is administered, preparations should be made for shock or anaphylactoid reactions, etc., and emergency measures should be on standby. With a drug in the same class, it has been reported that delayed adverse reactions (such as pyrexia, rash, nausea, decreased blood pressure or dyspnoea etc.) also occur an hour to several days after initiation of administration. Patients should be carefully observed after administration. Appropriate measures, including advising patients to immediately contact the attending physicians etc. in the event of such symptoms, should be taken.
- (2) Prior to use, patients should be carefully interviewed to assess any allergic disposition such as bronchial asthma, etc.
- (3) PROHANCE should be administered carefully after thoroughly evaluating patient renal function when administering the drug to patients with a renal function disorder or potentially compromised renal function.
- (4) It has been reported that patients with end-stage renal function disorders receiving long-term haemodialysis, chronic renal function disorders with estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73m<sup>2</sup> or acute renal failure have an increased risk of nephrogenic systemic fibrosis associated with the use of gadolinium-based contrast media. It is rec-

ommended to avoid the use of PROHANCE and to use alternative procedures.

- (5) The contrast effect usually continues for about 45 min directly after administration. Since additional administration does not always improve the contrast, PROHANCE should not be needlessly administered while contrast is still being achieved (except for patients suspected of having a metastatic brain tumor).

Additional administration of PROHANCE to patients suspected of having a metastatic brain tumor should be determined based on the radiographic efficacy of the initial administration.

### 3. Adverse Reactions

Adverse reactions were reported in 191 of 7,992 patients (2.39%). The most frequently observed adverse reactions were nausea in 86 patients (1.08%), vomiting in 34 patients (0.43%), elevation of ALT (GPT) in 13 patients (0.16%), abnormal hepatic function in 10 patients (0.13%), urticaria in 9 patients (0.11 %), elevation of AST (GOT) in 9 patients (0.11%) and leucocytosis in 9 patients (0.11%) (At the end of the reexamination period).

#### (1) Clinically significant adverse reactions

##### 1) Shock and anaphylactoid reactions

Shock (<0.1%) may occur. Since shock may accompany anaphylactoid reactions such as dyspnea, syncope, stupor, loss of consciousness, respiratory arrest, cardiac arrest, generalized redness, angioedema or urticaria, patients should be carefully observed after administration. In the event of such symptoms, appropriate measures should be taken.

[With an analogue gadolinium-compound (dimeglumine gadopentetate) used as a contrast medium for MRI, it has been reported that serious adverse reactions such as shock or anaphylactoid reactions may occur and that there is a higher chance with bronchial asthmatic patients than other patients.]

##### 2) Convulsive seizures

Convulsive seizures (<0.1%) may occur. In the event of such symptoms, appropriate measures, such as administration of barbituric acid (phenobarbital, etc.) or diazepam should be taken.

##### 3) Nephrogenic Systemic Fibrosis, NSF:

In some countries other than Japan, it has been reported that Nephrogenic Systemic Fibrosis (NSF) occurred in patients who had serious renal function disorders, after administration of PROHANCE. Patients should be carefully observed after administration for symptoms such as itching, swelling and sclerosis of the skin, joint stiffness or muscular weakness.

#### (2) Other adverse reactions

Patients should be carefully observed for the following symptoms and appropriate measures taken, if necessary.

	5% > ≥0.1%	<0.1%	Incidence unknown
Hypersensitivity	Urticaria	Rash, flushing, hot flushes and itching	
Cardiovascular		Palpitations	Decreased blood pressure, increased blood pressure
Respiratory		Coughing and sneezing	Hoarseness, pharyngolaryngeal symptoms, rhinitis and asthma
Gastrointestinal	Nausea/vomiting	Thirst	Abdominal pain
Psychoneurologic		Dizziness, headache and numbness	Tremors, temporary loss of consciousness
Hematologic	Leucocytosis	Thrombocytosis	
Liver and biliary system	Abnormal hepatic function, elevation of ALT (GPT) and elevation of AST (GOT)		
Injection site		Injection site vascular pain	Pain
Others		Feeling of warmth, feeling ill, chest pain, decrease in serum iron, elevation of serum potassium, elevation of BUN and elevation of blood creatinine	Feeling of cold, increased sweating, taste abnormality and eye abnormalities, malaise

#### 4. Use in the Elderly

Since the elderly often have a physiological hypofunction, they should be carefully observed when PROHANCE is administered to them.

#### 5. Use during Pregnancy, Delivery or Lactation

(1) PROHANCE should only be used in pregnant women or women suspected of being pregnant provided that the expected diagnostic benefits are evaluated to outweigh the possible risk of treatment.

[The safety of PROHANCE in pregnant women has not been established.]

(2) Nursing mothers should discontinue breast feeding during treatment.

[In animal studies (rats, i.v.), it has been reported that PROHANCE is excreted in breast milk.]

#### 6. Pediatric Use

Safety in low birth weight infants, newborns, nursing infants, infants and children has not been established (insufficient clinical experience).

#### 7. Precautions concerning Use

(1) Route of administration

PROHANCE should not be administered into the brain and spinal canal.

(2) Administration

1) Vascular pain may occur after intravenous administration of PROHANCE.

2) Since redness, swelling, blister, pain or other symptoms may occur when contrast media leak out of a vascular vessel, PROHANCE should be administered carefully.

(3) After opening

The contents of any one vial should only be used for one particular examination, and any amount remaining should be discarded.

#### PHARMACOKINETICS

When PROHANCE was administered intravenously to healthy adult male volunteers at doses of 0.1, 0.2, 0.4<sup>(note)</sup>, 0.5<sup>(note)</sup>, and 0.6<sup>(note)</sup> mL/kg (0.05, 0.1, 0.2, 0.25, and 0.3 mmol/kg, respectively), the elimination half-life from blood was estimated to be 1.09-1.66 hr, and the urinary excretion rate within 24 hr of administration accounted for 84.8-106.8% of the dose.<sup>1-2)</sup>

Note) Single doses of 0.4, 0.5 and 0.6 mL/kg are unapproved.

#### CLINICAL STUDIES

##### Contrast enhancing efficacy

(1) In clinical trials on 200 patients with brain or spinal diseases, the contrast enhancing efficacy evaluated at the approved dosage was 71.5% (143/200).<sup>3,4)</sup>

(2) In a clinical trial on 139 patients suspected of having metastatic brain tumor, the diagnostic quality was improved in 30.0% (21/70) by administering PROHANCE at a dose of 0.2 mL/kg, then giving an additional dose of 0.2 mL/kg.<sup>5)</sup>

(3) In clinical trials conducted on patients for examinations of the head, trunk and limbs, the contrast enhancing efficacy was 88.6% (39/44) for the head and neck, 89.6% (43/48) for the chest, 95.7% (44/46) for the heart, 95.6% (131/137) for the liver, 89.1% (41/46) for the kidney, 84.1% (37/44) for the pelvic area and 82.4% (42/51) for the bones and soft tissues.<sup>6,7,8)</sup>

The dose-response relationship at the approved dose, at half and double this (unapproved doses, respectively) was investigated in a phase II clinical trial. In the results, however, there was not necessarily good correlation between dose and response for all areas. The results of clinical trials are summarized in the following.

##### 1) Phase II clinical trial

When the contrast enhancing efficacy in a dose-response trial in 392 patients was evaluated according to six categories as “remarkably enhanced”, “enhanced”, “fairly enhanced”, “unchanged”, “decreased” and “impossible to evaluate”, the sums of “remarkably enhanced” and “enhanced” for different areas were as shown in the table below.

**The contrast enhancing efficacy**

Region	Dose (mL/kg)	sum of “remarkably enhanced” and “enhanced”
Head and neck	0.1	83.3% (15/18)
	0.2 <sup>note)</sup>	94.1% (16/17)
	0.4	88.9% (16/18)
Chest	0.1	60.0% (12/20)
	0.2 <sup>note)</sup>	78.9% (15/19)
	0.4	94.7% (18/19)
Heart	0.1	80.0% (16/20)
	0.2 <sup>note)</sup>	89.5% (17/19)
	0.4	59.1% (13/22)
Liver	0.1	42.1% (8/19)
	0.2 <sup>note)</sup>	84.2% (16/19)
	0.4	89.5% (17/19)

Region	Dose (mL/kg)	sum of "remarkably enhanced" and "enhanced"
Pelvic area	0.1	66.7% (12/18)
	0.2 <sup>note)</sup>	87.5% (14/16)
	0.4	93.8% (15/16)
Bone and soft tissue	0.1	61.1% (11/18)
	0.2 <sup>note)</sup>	83.3% (15/18)
	0.4	78.9% (15/19)
Kidney	0.05	57.9% (11/19)
	0.1 <sup>note)</sup>	85.0% (17/20)
	0.2	78.9% (15/19)

Note) Approved dosage

When the improvement of diagnostic quality in 328 patients was evaluated according to five categories as "remarkably improved", "improved", "fairly improved", "not improved" and "impossible to evaluate", the sums of "remarkably improved" and "improved" for different areas, were as shown in the table below. The diagnostic significance of these results is also indicated.

#### Diagnostic significance

Region	Dose (mL/kg)	A	B	C	D	E	F	Cases
Head and neck	0.1	0	3	12	8	2	0	16
	0.2 <sup>note)</sup>	0	5	11	1	2	0	13
	0.4	0	5	13	7	2	0	16
Chest	0.1	0	4	11	11	2	0	14
	0.2 <sup>note)</sup>	0	2	9	11	4	0	14
	0.4	0	3	14	12	3	0	17
Heart	0.1	0	10	15	3	2	0	16
	0.2 <sup>note)</sup>	0	14	18	3	0	1	19
	0.4	1	10	16	3	1	1	19
Liver	0.1	1	2	1	8	12	0	13
	0.2 <sup>note)</sup>	2	7	7	11	14	1	17
	0.4	2	10	10	10	13	0	18
Pelvic area	0.1	1	5	9	5	6	0	13
	0.2 <sup>note)</sup>	0	3	4	4	5	0	13
	0.4	1	5	7	8	5	0	16
Bone and soft tissue	0.1	0	3	7	11	8	1	12
	0.2 <sup>note)</sup>	0	6	13	13	8	2	17
	0.4	2	6	10	13	9	1	15
Kidney	0.05	0	4	5	7	5	0	14
	0.1 <sup>note)</sup>	0	5	9	14	5	0	18
	0.2	2	9	8	10	2	0	18

Diagnostic significance was determined by multiple choice.

Note) Approved dosage

A: Detection of new lesion

B: Clarification of lesion presence

C: Extension/Clarification of extent

D: Clarification of inner structure

F: Other

E: Discriminative diagnosis

### 2) Phase III controlled clinical trial

A controlled clinical trial was conducted to compare the global efficacy of gadoteridol with that of dimeglumine gadopentate in the hepatic region, evaluating contrast enhancing efficacy according to five categories as "remarkably effective", "effective", "fairly effective", "ineffective" and "impossible to evaluate". The sums of "remarkably effective" and "effective" were as shown in the table below. The results verified gadoteridol to be equivalent to dimeglumine gadopentate in terms of contrast enhancement.

#### Global evaluation of efficacy

(conducted by "evaluation committee")

Drug	Sum of "remarkably effective" and "effective"	Exact test
Gadoteridol	96.6% (114/118)	p=0.539
Dimeglumine gadopentate	94.2% (113/120)	

### 3) Phase III open labelled clinical trial

A global efficacy evaluation considering the contrast enhancing effect and improvement of diagnostic quality was conducted on 170 patients in an open labelled clinical trial, evaluating efficacy according to five categories as "remarkably effective", "effective", "fairly effective", "ineffective" and "impossible to evaluate". The sums of "remarkably effective" and "effective" were as shown in the table below.

#### Global evaluation of efficacy

Region	Sum of "remarkably effective" and "effective"
Head and neck	85.2% (23/27)
Chest	93.1% (27/29)
Heart	92.6% (25/27)
Pelvic area	85.7% (24/28)
Bone and soft tissue	78.8% (26/33)
Kidney	88.5% (23/26)

## PHYSICOCHEMISTRY

Nonproprietary name: Gadoteridol

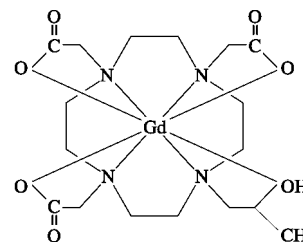
Chemical name:

(±)-10 (2-hydroxypropyl) -1, 4, 7, 10-tetraazacyclo-dodecane -1, 4, 7-triacetatogadolinium [III]

Molecular formula: C<sub>17</sub>H<sub>29</sub>GdN<sub>4</sub>O<sub>7</sub>

Molecular weight: 558.69

Structural formula:



#### Description:

Gadoteridol occurs as a white crystalline powder. It is odorless. It is very soluble in water, slightly soluble in ethanol (95), and practically insoluble in diethyl ether.

A solution of water in gadoteridol (1 in 100) shows no optical rotation.

## PACKAGING

**PROHANCE for Intravenous Injection 5 mL:**

Boxes of 5 vials

**PROHANCE for Intravenous Injection 10 mL:**

Boxes of 5 vials

**PROHANCE for Intravenous Injection 15 mL:**

Boxes of 5 vials

**PROHANCE for Intravenous Injection 20 mL:**

Boxes of 5 vials

**PROHANCE for Intravenous Injection Syringe 13 mL:**

Boxes of 1 syringe

**PROHANCE for Intravenous Injection Syringe 13 mL:**

Boxes of 5 syringes

**PROHANCE for Intravenous Injection Syringe 17 mL:**

Boxes of 1 syringe

**PROHANCE for Intravenous Injection Syringe 17 mL:**

Boxes of 5 syringes

**REFERENCES**

- 1) Yoshikawa H. et al.: Med. Consult. New Remed.,  
**28**, 803, 1991.
- 2) Shibata H. et al.: *ibid.*, **30**, 1863, 1993.
- 3) Yoshikawa H. et al.: *ibid.*, **28**, 1987, 1991.
- 4) Yoshikawa H. et al.: *ibid.*, **29**, 1119, 1992.
- 5) Kourogi M. et al.: *ibid.*, **31**, 1361, 1994.
- 6) Naito H. et al. : *ibid.*, **32**, 715, 1995.
- 7) Naito H. et al. : *ibid.*, **33**, 217, 1996.
- 8) Hirohashi S. : *ibid.*, **33**, 233, 1996.

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