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Since this translation is prepared in June 2024 based on the Japanese text current at that time, the translation may not reflect the latest information, due to continuous revision of package inserts.

The latest Japanese text is available on PMDA website.

Revised: June 2024 (4rd version of new form)

Standard Commodity Classification Number of Japan
87729

Storage: Room temperature
Shelf Life: 3 years
Therapeutic Category: Macrocyclic non-ionic contrast agent for MRI
Regulatory Classification: Prescription-only drug [Note)]

Note) Use only as directed by a physician.

	IV injection 5mL	IV injection 10mL	IV injection 15mL
Approval Number.	22100AMX00462000	22100AMX00499000	22100AMX00500000
Date of Initial Marketing in Japan	July 1994	January 1997	July 1994

	IV injection 20mL	IV syringe 13mL	IV syringe 17mL
Approval Number.	22100AMX00461000	22100AMX00463000	22100AMX00464000
Date of Initial Marketing in Japan	July 1994	July 2002	

Gadoteridol solution for injection

ProHance® intravenous injection 5mL
ProHance® intravenous injection 10mL
ProHance® intravenous injection 15mL
ProHance® intravenous injection 20mL
ProHance® intravenous syringe 13mL
ProHance® intravenous syringe 17mL

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1. WARNINGS

1.1 Do not administer this drug into the brain or medullary cavity because its administration through this route may cause serious adverse reactions. [see 14.1.1]

1.2 Pay special attention to patients with renal impairment or suspected impaired renal function because increased risk of nephrogenic systemic fibrosis due to gadolinium-based contrast agents has been reported in patients with serious renal impairment. [see 9.2.1-9.2.3, 11.1.3]

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)

2.1 Patients with a history of serious adverse reactions to this drug [Serious adverse reactions may recur.]

2.2 Patients with a history of hypersensitivity to ingredients of this drug or gadolinium-based contrast agents

3. COMPOSITION AND PRODUCT DESCRIPTION

3.1 Composition

Each vial or syringe contains the following ingredients:

Brand name		ProHance intravenous injection				ProHance intravenous syringe	
		5mL	10mL	15mL	20mL	13mL	17mL
Active ingredient	Gadoteridol	1396.5mg	2793.0mg	4189.5mg	5586.0mg	3630.90mg	4748.10mg
Excipients	Calteridol calcium	1.15mg	2.30mg	3.45mg	4.60mg	2.99mg	3.91mg

	Trometamol	6.05mg	12.10mg	18.15mg	24.20mg	15.73mg	20.57mg
	Hydrochloric acid	Adequate dose					
	Sodium hydroxide	Adequate dose					

3.2 Product Description

Brand name	ProHance intravenous injection				ProHance intravenous syringe	
	5mL	10mL	15mL	20mL	13mL	17mL
Description	Colorless and clear solution					
pH	6.5 - 8.0					
Osmotic pressure ratio (ratio relative to isotonic sodium chloride solution)	Approximately 2					
Viscosity (37℃, mPa・s)	1.3					

4. INDICATIONS

Contrast enhancement in magnetic resonance imaging (MRI) of following lesion:

○Brain and spinal cord

○Trunk and extremities

5. PRECAUTIONS CONCERNING INDICATIONS

The necessity of examinations using gadolinium-based contrast agents should be carefully evaluated because there have been reports of high signal in the brain sections including dentate nucleus of cerebellum and globus pallidus on unenhanced T1-weighted MR images and detection of gadolinium in autopsied brain tissues in patients who received multiple doses of gadolinium-based contrast agents.

6. DOSAGE AND ADMINISTRATION

<General (except kidney imaging)>

The usual dose in adult patients is 0.2 mL/kg administered by intravenous injection.

In patients with suspicion of having metastases to brain, additional dose of 0.2 mL/kg can be administered within 30 minutes after administration of the initial dose of 0.2 mL/kg, in case of no tumor is detected or imaging efficacy is insufficient even if a tumor is detected.

<Kidney imaging>

The dose in adult patients is 0.1 mL/kg administered by intravenous injection.

8. IMPORTANT PRECAUTIONS

8.1 Serious adverse reactions such as shock and anaphylaxis may occur. For administering this drug, make sure appropriate emergency measures should be immediately available. Continuously monitor patients' condition carefully even after administration because delayed adverse reactions (such as pyrexia, rash, nausea, blood pressure decreased, dyspnoea, etc.) which may occur from one hour to several days after from the initiation of administration have been reported in other gadolinium-based contrast agents. Take appropriate measures such as instructing patients to immediately contact the attending physicians or other healthcare professionals if any of the aforementioned symptoms occur. [see 11.1.1]

8.2 Patients should be carefully interviewed focusing on allergic predispositions such as bronchial asthma before administering this drug. [see 9.1.2, 9.1.4-9.1.6]

8.3 Contrast enhanced effect is usually continued for about 45 minutes from immediately after administration of this drug. Do not administer any additional dose without a specific reason while the effect is continued because an additional dose does not always improve the effect (except patients with suspicion of having metastases to brain). The decision to give additional dose to patients with suspicion of having metastases to brain should be based on the results of the initial dose. [see 17.1.3]

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.1 Patients with Complication or History of Diseases, etc.

9.1.1 Patients with an extremely poor general condition

Do not administer this drug unless it is deemed unavoidable for diagnosis.

9.1.2 Patients with bronchial asthma

Do not administer this drug unless it is deemed unavoidable for diagnosis. Anaphylaxis may occur.

It has been reported that other gadolinium-based contrast agents for MRI (gadopentetate dimeglumine) may cause serious adverse reactions such as shock or anaphylaxis in patients with bronchial asthma at a higher frequency than in other patients. [see 8.2, 11.1.1]

9.1.3 Patients experienced adverse reactions (excluding serious adverse reactions) at the initial dose and need to be given additional dose

Do not administer this drug unless it is deemed unavoidable for diagnosis.

9.1.4 Patients with allergic predispositions such as allergic rhinitis, rash or urticaria, etc.

[see 8.2]

9.1.5 Patients whose parents or siblings have allergic predisposition, such as bronchial asthma, allergic rhinitis, rash or urticaria, etc.

[see 8.2]

9.1.6 Patients with a history of drug hypersensitivity

[see 8.2]

9.1.7 Patients with convulsion or epilepsy including a history, or with predisposition to them

Convulsion may occur. [see 11.1.2]

9.2 Patients with Renal Impairment

9.2.1 Patients with serious renal impairment

Do not administer this drug unless it is deemed unavoidable for diagnosis.

Since this drug is excreted mainly through the kidneys, the excretion may be delayed and renal function may be aggravated. [see 1.2, 11.1.3]

9.2.2 Patients with end-stage renal impairment on long-term dialysis, chronic renal impairment with eGFR (estimated glomerular filtration rate) of less than 30 mL/min/1.73m^2, or acute renal impairment (except patients with serious renal impairment)

It is desirable to avoid administration of this drug and substitute other examination.

Risk of occurrence of nephrogenic systemic fibrosis due to gadolinium-based contrast agents has been reported to be increased. [see 1.2, 11.1.3]

9.2.3 Patients with renal impairment or suspicion of having impaired renal function (except patients with serious renal impairment)

This drug should be administered with caution after carefully assessing the patient's renal function. [see 1.2, 11.1.3]

9.5 Pregnant Women

Administration of this drug to women who are or may be pregnant should be limited to the case in which the diagnostic benefit is considered to surpass the risk.

9.6 Brest-feeding Women

Diagnostic benefit using this drug and the benefit of breast milk nutrients should be weighed for consideration of continuing or discontinuing breastfeeding.

Excretion of this drug into breast milk has been reported in animal studies (rats, intravenous administration).

9.7 Pediatric Use

No clinical study has been conducted in pediatric patients.

9.8 Geriatric Use

This drug should be administered to the elderly patients with careful monitoring.

The elderly have reduced physiological condition in general.

11. ADVERSE REACTIONS

Following adverse reactions may occur. Monitor patients' condition carefully and take appropriate measures such as

discontinuing the administration if any abnormalities are observed.

11.1 Clinically Significant Adverse Reactions

11.1.1 Shock and anaphylaxis (frequency unknown for both)

Shock may occur, and be accompanied by anaphylaxis with symptoms of such as dyspnoea, syncope, stupor, loss of consciousness, respiratory arrest, cardiac arrest, generalized flushing, angioedema, and urticaria. [see 8.1, 9.1.2]

11.1.2 Seizure (frequency less than 0.1%)

Take appropriate measures such as administering barbituric acid derivatives including phenobarbital or diazepam. [see 9.1.7]

11.1.3 Nephrogenic systemic fibrosis (NSF) (frequency unknown)

The occurrence of NSF has been reported after administration of this drug to patients with serious renal impairment in other countries. Careful monitoring should be continued after administration of this drug and with particular attention to the occurrence of abnormalities such as itchy skin, swelling, hardening of skin, joint stiffness, and muscular weakness. [see 1.2, 9.2.1-9.2.3]

11.2 Other Adverse Reactions

	≥ 0.1% < 5%	< 0.1%	Frequency unknown
Hypersensitivity	Urticaria	Hot flush	Itching, Rash, Flushing
Cardiovascular disorders			Palpitations, Blood pressure decreased, Blood pressure increased
Respiratory disorders		Cough	Sneezing, Hoarseness, Pharyngolaryngeal discomfort, Rhinitis, Asthma
Gastrointestinal disorders	Queasy/Vomiting		Thirst, Abdominal pain
Psychoneurotic disorders		Giddiness, Headache	Numbness, Tremors, Transient loss of consciousness
Hematology investigations			White blood cell increased, Platelets increased
Hepatobiliary disorders			Hepatic function abnormal, AST increased, ALT increased
Administration site conditions		Vascular pain	Pain
Others	Feeling hot		Serum potassium increased, Feels poorly, BUN increased, Chest pain, Serum iron decreased, Blood creatinine increased, Feeling cold, Heavy sweating, Taste abnormality, Eye abnormality, Malaise

14. PRECAUTIONS CONCERNING USE

14.1 Precautions Concerning Administration of the Drug

14.1.1 Do not administer this drug into the brain or medullary cavity. [see 1.1]

14.1.2 Vascular pain may occur after intravenous administration of this drug.

14.1.3 In case extravasation of contrast media occur, patient may develop redness, swelling, blister, or pain, etc. Extreme caution during administration is necessary to avoid extravasation.

14.2 Precautions Concerning Post-Administration of the Drug

Use each vial/syringe for a single examination and discard excess solution.

16. PHARMACOKINETICS

16.1 Blood Level

A dose of 0.1, 0.2, 0.4 Note), 0.5 Note) or 0.6 Note) mL/kg (0.05, 0.1, 0.2, 0.25 or 0.3 mmol/kg) of this drug was

administered intravenously to healthy male volunteer, the elimination half-life in blood was 1.09-1.66 hours. [1), 2)]

Note) The approved dose of this drug is 0.2 mL/kg (0.1 mmol/kg) for general use and 0.1 mL/kg (0.05 mmol/kg) for kidney imaging.

16.5 Excretion

A dose of 0.1, 0.2, 0.4 [Note)], 0.5 [Note)] or 0.6 [Note)] mL/kg (0.05, 0.1, 0.2, 0.25 or 0.3 mmol/kg) of this drug was administered intravenously to healthy male volunteer, 84.8-106.8% of the dose was excreted in urine within 24 hours after administration. [1), 2)]

Note) The approved dose of this drug is 0.2 mL/kg (0.1 mmol/kg) for general use and 0.1 mL/kg (0.05 mmol/kg) for kidney imaging.

17. CLINICAL STUDIES

17.1 Clinical Studies for Efficacy and Safety

<MRI of brain and spinal cord>

17.1.1 Domestic phase II clinical study

The efficacy rate was 71.8% (56/78) in 78 evaluable patients for contrast efficacy at the approved dose. Adverse reactions were observed in 2.4% (2/84), both of them were queasy. [3)]

17.1.2 Domestic phase III clinical study

The efficacy rate was 71.3% (87/122) in 122 evaluable patients for contrast efficacy at the approved dose. Adverse reactions were observed in 2.3% (3/130) with one patient each of feeling hot/nausea, vomiting, and nausea. [4)]

17.1.3 Domestic phase II/III clinical study

In clinical study in patients with suspicion of having metastases to brain, diagnostic performance was improved in 30.0% (21/70) of patients among who received initial dose of 0.2 mL/kg followed by an additional 0.2 mL/kg in comparison with the initial dose. Adverse reactions were observed in 2.8% (2/72), and with one patient each of convulsions and feeling hot/queasy. [5)] [see 8.3]

<MRI of trunk and extremities>

17.1.4 Domestic phase II clinical study

In a dose-finding study conducted in 400 patients (three groups: approved dose, half of the approved dose, or double of the approved dose), contrast enhanced efficacy was assessed in 392 patients subject to efficacy evaluation using 6 scales: markedly enhanced, enhanced, slightly enhanced, unchanged, decreased, and unevaluable, those rated as "enhanced" or better are shown in Table 1. There was no dose-response relationship in the efficacy of this drug on the some examination regions.

Table 1. Contrast enhanced efficacy

Examination region	Dose (mL/kg)	"Enhanced" or better
Head and neck	0.1	83.3% (15 / 18)
	0.2 [Note)]	94.1% (16 / 17)
	0.4	88.9% (16 / 18)
Chest	0.1	60.0% (12 / 20)
	0.2 [Note)]	78.9% (15 / 19)
	0.4	94.7% (18 / 19)
Heart	0.1	80.0% (16 / 20)
	0.2 [Note)]	89.5% (17 / 19)
	0.4	59.1% (13 / 22)
Liver	0.1	42.1% (8 / 19)
	0.2 [Note)]	84.2% (16 / 19)
	0.4	89.5% (17 / 19)
Intrapelvic	0.1	66.7% (12 / 18)
	0.2 [Note)]	87.5% (14 / 16)
	0.4	93.8% (15 / 16)

Bone and soft tissue	0.1	61.1% (11 / 18)
	0.2 Note)	83.3% (15 / 18)
	0.4	78.9% (15 / 19)
Kidneys	0.05	57.9% (11 / 19)
	0.1 Note)	85.0% (17 / 20)
	0.2	78.9% (15 / 19)

Note) Approved dose

Improvement in diagnostic performance was rated using 5 scales: markedly improved, improved, slightly improved, not improved, and unevaluable. The details of improved diagnostic performance in 328 patients rated as "improved" or better are shown in Table 2.

Table 2. Improvement in diagnostic performance

Examination 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 Note)	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 Note)	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 Note)	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 Note)	2	7	7	11	14	1	17
	0.4	2	10	10	10	13	0	18
Intrapelvic	0.1	1	5	9	5	6	0	13
	0.2 Note)	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 Note)	0	6	13	13	8	2	17
	0.4	2	6	10	13	9	1	15
Kidneys	0.05	0	4	5	7	5	0	14
	0.1 Note)	0	5	9	14	5	0	18
	0.2	2	9	8	10	2	0	18

Multiple selection was permitted for evaluation of improvement in diagnostic performance.
Note) Approved dose
A: Detection of new lesions
B: Clarification of the presence of lesions
C: Clarification of the range of spread/progression
D: Clarification of internal structure
E: Differential diagnosis
F: Others

Adverse reactions were occurred in 1.3% (5/397) of patients: queasy/vomiting and urticaria in one patient each in approved dose group, nausea and queasy in one and two patients respectively in the double dose group. [6)]

17.1.5 Domestic phase III comparative study

In the comparative study with gadopentetate dimeglumine focusing on hepatic region, overall evaluation (efficacy) was assessed using 5 scales: markedly effective, effective, slightly effective, ineffective and unevaluable, those assessed as "effective" or better are shown in Table 3. The equivalence of this drug to gadopentetate dimeglumine was verified. No adverse reaction was reported in the gadoteridol group (122 patients). [7)]

Table 3. Overall evaluation (Efficacy) (Assessment by image reading committee)

Drug	"Effective" or better	Exact test
Gadoteridol	96.6% (114 / 118)	p = 0.539
Gadopentetate dimeglumine	94.2% (113 / 120)	

17.1.6 Domestic phase III open-label study

In open-label study conducted in 175 patients, overall evaluation (efficacy) considering contrast enhanced effect and improvement in diagnostic performance in 170 evaluable patients was assessed using 5 scales: markedly effective, effective, slightly effective, ineffective, and unevaluable, and those assessed as "effective" or better are shown in Table 4. Adverse reactions occurred in 3.5% (6/171) of patients: queasy in 2 patients and flushed face/cough, feeling hot, nausea, and injection site vascular pain in one patient each. [8)]

Table 4. Overall evaluation (Efficacy)

Examination region	"Effective" or better
Head and neck	85.2% (23 / 27)
Chest	93.1% (27 / 29)
Heart	92.6% (25 / 27)
Intrapelvic	85.7% (24 / 28)
Bone and soft tissue	78.8% (26 / 33)
Kidneys	88.5% (23 / 26)

18. PHARMACOLOGY

18.1 Mechanism of Contrast Enhancement

Gadolinium ions are paramagnetic and have the ability to promote relaxation of hydrogen nuclei (protons) in magnetic resonance phenomenon and shorten relaxation time.

This drug is a chelate compound of paramagnetic metal gadolinium ions that enhances contrast of tissues and lesions by shortening the longitudinal relaxation time (T1) in MRI imaging.

19. PHYSICOCHEMICAL PROPERTIES

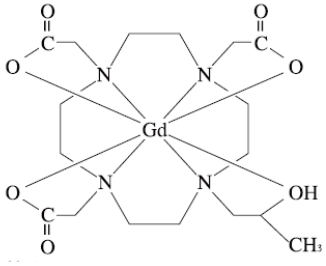
Nonproprietary name: Gadoteridol

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

Molecular formula: $C_{17}H_{29}GdN_4O_7$

Molecular weight: 558.68

Structural formula:



Physicochemical description:

Gadoteridol is a white crystalline powder, and it is odorless. It is highly water-soluble, and slightly soluble in ethanol (95) and practically insoluble in diethyl ether.

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

22. PACKAGING

<ProHance intravenous injection 5mL>

Boxes of 5 vials

<ProHance intravenous injection 10mL>

Boxes of 5 vials

<ProHance intravenous injection 15mL>

Boxes of 5 vials

<ProHance intravenous injection 20mL>

Boxes of 5 vials

<ProHance intravenous syringe 13mL>

Boxes of 1 or 5 syringes

<ProHance intravenous syringe 17mL>

Boxes of 1 or 5 syringes

23. REFERENCES

1) Yoshikawa H. et al., Med Cons New-Remed. 1991; 28(5): 803-812 [PRO-0061]

2) Shibata H. et al., Med Cons New-Remed. 1993; 30(10): 1863-1872 [PRO-0073]

3) Yoshikawa H. et al., Med Cons New-Remed. 1991; 28(11): 1987-1999 [PRO-0062]

[PRO-0063]

4) Yoshikawa H. et al., Med Cons New-Remed. 1992; 29(5): 1119-1137 [PRO-0069]

5) Kohro M. et al., Med Cons New-Remed. 1994; 31(8): 1361-1376 [PRO-0084]

6) Naito H. et al., Med Cons New-Remed. 1995; 32(4): 715-737 [PRO-0077]

7) Hirohashi S. et al., Med Cons New-Remed. 1996; 33(2): 233-245 [PRO-0076]

8) Naito H. et al., Med Cons New-Remed. 1996; 33(2): 217-232

24. REFERENCE REQUEST AND CONTACT INFORMATION

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1-13-21, Minamiikebukuro, Toshima-ku, Tokyo,171-0022, Japan

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26. MARKETING AUTHORIZATION HOLDER, etc.

26.1 Marketing Authorization Holder (Importer)

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1-13-21, Minamiikebukuro, Toshima-ku, Tokyo, Japan

26.2 Licensed by:

Bracco Suisse S.A.