[Approved date] YY MM DD

Package Insert for Gadobutrol Injection

Please carefully read the package insert and use under the guidance of a physician

Warning: Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF is a fibrotic disease characterized by damage to the skin, muscles or internal organs, which affects life functions and is even fatal.

The risk for NSF is highest among the following patients:

-With acute or chronic severe renal insufficiency (GFR < 30 mL/min/1.73 m^2), or

–-With any degree of acute renal insufficiency due to hepatorenal syndrome or during liver transplantation

Before use, it is recommended to screen all such patients to determine whether there is renal insufficiency by medical history inquiry and/or laboratory tests.

Gadolinium deposition

Both linear and macrocyclic gadolinium-based contrast agents (GBCAs) will deposit trace amounts of gadolinium in the brain and other tissues. Animal experiments have shown that after repeated use of GBCAs, the deposition of linear GBCAs is higher than that of macrocyclics. This product is macrocyclic GBCAs.

[Drug Name]

Generic name: Gadobutrol Injection

English name: Gadobutrol Injection

Chinese pinyin: Gabuchun Zhusheye

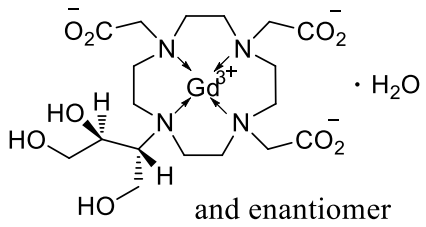
[Ingredient]

The active ingredient is gadobutrol.

Chemical name: (10-(2,3-dihydroxy-1-(hydroxymethyl)

propyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, gadolinium complex

Chemical structural formula:



and enantiomer

Molecular formula: $C_{18}H_{31}GdN_4O_9 \cdot H_2O$

Molecular weight: 622.73

[Excipients]

Calcobutrol, tromethamine, sodium hydroxide, hydrochloric acid, water for injection

[Description]

The product is colorless clear liquid.

[Indication]

For diagnosis, only for intravenous administration.

Contrast-enhanced magnetic resonance imaging (CE-MRI) examination of lesions in various parts of the body (including the brain and spinal cord);

Contrast-enhanced magnetic resonance angiography (CE-MRA) of various parts of the body.

[Strength]

7.5 ml: 4.5354 g

[Dosage and Administration]

Gadobutrol injection should be administered by a physician with clinical experience in MRI.

Administration

Use rapid intravenous injection to give the required dose. MRI contrast-enhanced scans can be started immediately after the administration (the interval depends on the pulse sequence and examination protocol used).

In contrast-enhanced magnetic resonance angiography (CE-MRA), the best imaging can be observed in the arterial first-pass phase after injection of gadobutrol injection. In cases of MRI of the brain and spinal cord, the best imaging effect can be observed within about 15 minutes after the injection of gadobutrol injection (the interval depends on the type of lesion/tissue). Tissue enhancement usually lasts 45 minutes after the injection of gadobutrol.

T1-weighted scan sequence is particularly suitable for contrast-enhanced examinations.

When the contrast agent is administered by intravascular injection, if possible, the patient should lie supine. After the injection is completed, the patient should be observed for at least half an hour, because the experience of using the contrast agent shows that most of the adverse reactions occur within this period of time.

Dose

Use the lowest approved dose whenever possible.

Adults

MRI of the brain and spinal cord

The recommended dose for adults is 0.1 mmol/kg body weight, equivalent to 1.0 M solution 0.1 ml/kg body weight.

If there is no abnormality in the enhanced MRI scan and the presence of a lesion is still highly suspected in clinical practice, or more precise information is needed to guide the patient's treatment, up to 0.2 mmol/kg body weight gadobutrol injection can be injected again within 30 minutes after the first administration to improve the accuracy of diagnosis.

Whole body MRI (except MRA)

Generally, 0.1 ml gadobutrol injection/kg body weight is sufficient to meet clinical requirements.

Contrast-enhanced magnetic resonance angiography (CE-MRA)

Imaging with one field of view:

If the weight is less than 75 kg, use 7.5 ml; if the weight is greater than or equal to 75 kg, use 10 ml (equivalent to 0.1-0.15 mmol/kg body weight).

Imaging with more than one field of view:

If the weight is less than 75 kg, use 15 ml; if the weight is greater than or equal to 75 kg, use 20 ml (equivalent to 0.2-0.3 mmol/kg body weight).

Children

For children who have not received an electrocardiogram, the possibility of congenital long QT syndrome must be ruled out before administration of gadobutrol injection.

For the above indications, the recommended dose in children and adolescents aged 2 years and older is 0.1 mmol gadobutrol injection/kg body weight (equivalent to 0.1 ml/kg body weight).

Children and adolescents should not be given doses > 0.1 ml/kg body weight.

Due to the lack of effectiveness and safety data, gadobutrol injection is not recommended for patients under 2 years of age.

[Adverse Reactions]

Summary of safety characteristics

The overall safety characteristics of this product are based on clinical research data from more than 6300 patients and post-marketing monitoring data.

The most common adverse drug reactions (≥0.5%) observed in patients receiving this product were headache, nausea and dizziness.

The most serious adverse drug reactions observed in patients receiving this product were cardiac arrest and severe anaphylactoid reactions (including respiratory arrest and anaphylactic shock).

Delayed allergic reactions (a few hours or as long as a few days later) were rarely observed.

Most adverse reactions were mild to moderate.

List of adverse reactions

The adverse drug reactions observed with this product are listed in the table below. They are classified according to the system organ category (MedDRA). The most appropriate MedDRA terms are used to describe the identified reactions and their synonyms and related conditions.

The adverse drug reactions in clinical studies are divided by frequency of occurrence The frequency of occurrence is defined as follows: common: ≥1/100 to <1/10; uncommon: ≥1/1000 to <1/100; rare: ≥1/10000 to <1/1000. Reactions only found during the post-marketing monitoring period whose frequency cannot be estimated are listed under "Unknown".

In each frequency group, adverse reactions are ranked from high to low in severity.

Table 1: Adverse drug reactions of patients reported in clinical studies or post-marketing monitoring

System organ class	**Common**	**Uncommon**	**Rare**	**Unknown**
Immune system disorders		Hypersensitivity/anaphylactoid reaction*# (e.g., anaphylactic shock§*, circulatory failure§*, respiratory arrest§*, pulmonary edema§*, bronchospasm§, cyanosis§, oropharyngeal swelling§*, laryngeal edema§, hypotension, blood pressure increased§, chest pain§, urticaria, facial edema, angioedema§, conjunctivitis§, eyelid edema, flushing, hyperhidrosis, cough, sneezing, burning, looked pale)		

Nervous system disorders	Headache	Dizziness Taste disorders Paraesthesia	Loss of consciousness* Convulsions* Parosmia	
Heart disease			Tachycardia* Palpitations	Cardiac arrest*
Respiratory, chest and mediastinal disorders		Dyspnea*		
Gastrointestinal disorders	Nausea	Vomiting	Dry mouth	
Skin and subcutaneous tissue disorders		Erythema Pruritus (including generalized pruritus) Skin rashes (including generalized, macular, papular, and pruritic rashes)		Nephrogenic Systemic Fibrosis (NSF)
General disorders and administration site conditions		Injection site reaction [0] Heat feelings	Discomfort Cold feelings	

* Life-threatening adverse events and/or AEs leading to fatal outcomes have been reported

[#] Among all the adverse drug reaction symptoms listed under the hypersensitivity/anaphylactoid reactions identified in clinical trials, except for urticaria, the frequencies of other adverse reactions are not higher than rare

[§] Hypersensitivity/anaphylactoid reactions were found only in the post-marketing monitoring period (frequencies unknown).

[0] Injection site reactions (different types) include the following terms: injection site discharge, injection site burning, injection site chills, injection site warmth, injection site redness or rash, injection site pain, and injection site hematoma

[Contraindications]

The product is contraindicated in those who are allergic to the product ingredients. Patients with allergic reactions to other gadolinium chelate or with a history of suspected allergic reactions shall not use the product.

[Precautions]

Effects on the ability to drive and operate machines

Unrelated

Incompatibility

Without compatibility test, this drug should not be used with other drugs.

Use/operation instructions

The drug should be visually inspected before use. If there is severe discoloration, particulate

matter or container damage, it should not be used.

Vial:

Do not draw gadobutrol injection into the syringe until immediately before use.

Do not pierce the rubber stopper more than once.

Discard any unused vial contents.

After the container is opened for the first time:

The physical and chemical properties remain stable within 24 hours at room temperature. From a microbiological perspective, the drug should be used immediately. If it cannot be used immediately, the user is responsible for ensuring the storage time and conditions before use. It should be stored at 2-8℃ for no more than 24 hours, unless it is opened under effectively controlled and verified sterile conditions.

GBCAs should be used with caution. When the corresponding critical diagnostic information is not available with non-contrast enhanced MRI, GBCAs can be used, and the lowest approved dose is recommended.

Gadolinium deposition

Current evidence shows that after repeated use of GBCAs, trace amounts of gadolinium can remain in the brain and other body tissues. Research reports have shown that multiple use of GBCAs can increase the intensity of brain signals, especially in the dentate nucleus and globus pallidus. Currently, there are more reports about linear GBCAs and fewer reports about macrocyclic GBCAs. Animal experiments have shown that the amount of gadolinium deposited after repeated use of linear GBCAs is higher than that of repeated use of macrocyclics.

The clinical significance of brain gadolinium deposition is unclear.

In order to minimize the potential risks associated with gadolinium deposition in the brain, it must be used in strict accordance with the indications and approved doses. It is recommended to use the lowest approved dose that meets the requirement of diagnosis and perform careful benefit risk assessment and patient informed communication before repeated administration. .

Special warnings

When gadobutrol injection is injected via a small-lumen vena cava, adverse reactions such as redness or swelling at the injection site may occur. The use of gadobutrol injection must comply with the usual safety regulations for magnetic resonance imaging. Ferromagnetic substances, in particular, are prohibited.

Allergy

Allergic reactions have been reported with other gadolinium-containing contrast agents, and similar reactions have been observed after the use of gadobutrol injection. In order to respond quickly to emergencies, drugs and equipment (such as endotracheal intubation, respirators) must be available at all times.

For patients known to be allergic to gadobutrol injection, the risks/benefits must be carefully assessed.

Like other intravenous contrast agents, gadobutrol injection can be accompanied by allergic/hypersensitivity reactions or other idiopathic reactions characterized by cardiovascular, respiratory, and skin manifestations, even including serious reactions such as shock. Under normal circumstances, patients with cardiovascular disease are prone to severe hypersensitivity reactions with serious or fatal outcomes.

In the event of the following conditions, the risk of allergic reactions will increase:

Past history of allergic reactions to contrast agents

History of bronchial asthma

History of allergic disease

For patients with allergic constitution, before deciding whether to use gadobutrol injection, the risks/benefits must be carefully assessed.

Most of these reactions occurred within half an hour after administration of the contrast agents.

Therefore, it is recommended to observe the patient after the operation.

Medical treatment of hypersensitivity reactions and establishment of first aid measures are necessary.

In rare cases, delayed reactions (a few hours to a few days later) have been observed. (see "Adverse Reactions")

As with other contrast-enhanced diagnostic procedures, it is recommended to observe the patient after the operation.

As with other diagnostic procedures, it is recommended to observe the patient after the operation.

Renal impairment

Before giving this product, patients should be screened through laboratory tests. In patients with severe renal impairment, the clearance of the contrast agent will be delayed, so the risks/benefits must be assessed carefully.

Before gadobutrol is administered to patients with kidney dysfunction again, it should be ensured that gadobutrol has been excreted by the kidneys within a sufficient period of time. Generally, complete recovery in the urine was seen in patients with mild or moderate renal impairment within 72 hours. In patients with severely impaired renal function at least 80% of the administered dose was recovered in the urine within 5 days (see [Pharmacokinetics]).

This product can be excreted from the body through hemodialysis. After three dialysis sessions, about 98% of the contrast agent will be excreted from the body. For patients undergoing dialysis, hemodialysis immediately after the administration of gadobutrol injection may help clear the drug from the body.

It has been reported that the occurrence of nephrogenic systemic fibrosis (NSF) is related to the use of some gadolinium-containing contrast agents (including this product) in the following patients.

Acute or chronic severe kidney injury (GFR＜30ml/min/1.73 m^2) or

Acute renal insufficiency caused by liver and kidney syndrome or perioperative period of liver transplantation.

Therefore, before using this product in the above patients, their risks/benefits must be carefully assessed (see [Adverse Reactions]). Nephrogenic systemic fibrosis is a progressive disease characterized by damage to the skin, muscles, and internal organs, which affects life functions, and sometimes is fatal. It mainly leads to the proliferation of connective tissue in the skin and internal organs, making the skin thickened, rough and stiff, sometimes leading to disabling contractures. Since the use of gadobutrol injection has the possibility of causing NSF, it should be avoided in patients with acute or chronic severe renal impairment (GFR< 30 ml/min/1.73 m^2) and patients with various degrees of liver and kidney syndrome caused by acute renal insufficiency or before and after liver transplantation. Unless the diagnostic information is necessary and cannot be obtained by other means, patients with severe renal impairment should not be given multiple doses in one scan. Due to the lack of information on repeated dosing, repeated dosing is not advised

unless there is an interval of at least 7 days between injections. For patients undergoing dialysis, hemodialysis immediately after the administration of gadobutrol injection may help clear the drug from the body, but its effect in preventing NSF is unknown. Therefore, it should not be used as a preventive measure for other patients.

The risk of nephrogenic systemic fibrosis in patients with moderate renal impairment (GFR 30-59 ml/min/1.73 m^2) is uncertain. Therefore, be vigilant when using this product in such patients. All patients should be screened through medical history and/or laboratory tests for renal insufficiency. When administering a gadolinium-containing contrast agent, do not exceed the recommended dose, and allow sufficient time for the drug to be cleared from the body before re-administration.

Effects on the heart: QTc interval prolongation

QTc interval prolongation may lead to an increased risk of ventricular arrhythmias, including torsades de pointes. It has been observed that with other drugs that prolong the QT interval, women are at a greater risk of developing torsades de pointes than men.

The risk increases. Other QTc interval prolongations observed

The risk of torsion ventricular tachycardia is greater.

In healthy volunteers, after injection of a dose (0.5-1.5 mmol/kg) higher than the clinically recommended dose of 0.3 mmol/kg, a dose-dependent QTc prolongation of >60 msec was observed in a relative high proportion of the population. Therefore, it is not recommended to use gadobutrol injection at doses higher than 0.3 mmol/kg. In the clinical study, 708 patients who used gadobutrol injection did not experience cardiovascular adverse reactions that caused QTc prolongation. However, certain pre-existing disease conditions or conditions may increase the risk of ventricular arrhythmia.

Administration of gadobutrol injection at high doses may prolong the QT interval in the ECG of some patients. Therefore, extreme care should be taken when using this product in patients known to have prolonged QT interval, patients with hypokalemia, and patients receiving Class IA (such as quinidine, procainamide) or Class III (such as amiodarone, sotalol) antiarrhythmic drugs, because there is a lack of clinical experience in these patients and the potential risks are unknown.

No studies have been conducted to compare the pharmacokinetics of gadobutrol injection with other drugs that prolong the QT interval, such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants. The interaction of gadobutrol injection with these drugs cannot be ruled out, so care should be taken when gadobutrol injection is co-administered with these drugs.

The effect of gadobutrol injection in patients with congenital QT prolongation has not been studied, but it is recommended that these individuals may be more sensitive to drugs-induced QT prolongation. Due to limited clinical experience, extreme caution should be exercised when using gadobutrol injection in patients have conditions that may cause arrhythmias, such as clinically significant bradycardia, acute myocardial ischemia, clinically relevant heart failure with reduced left ventricular ejection fraction, or a history of symptomatic arrhythmia, and the risks/benefits should be carefully assessed.

A careful risk assessment of potential cardiac effects is recommended. Patients with risk factors should be observed for at least one hour after the injection of gadobutrol injection, because transient effects may occur within the first few minutes after administration.

In order to ensure the safe and effective use of gadobutrol injection, patients should be informed of the following information and instructions:

1. Gadobutrol injection may cause changes in ECG (QTc interval prolongation).

2. If they are receiving Class IA (such as quinidine, procainamide) or Class III (such as amiodarone, sotalol) antiarrhythmic drugs, they should avoid using gadobutrol injection.
3. Gadobutrol injection may increase the QT interval-prolonging effect of other drugs such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants.
4. It is necessary to inform the physician about personal or family history of QT interval prolongation, or conditions that cause arrhythmia such as recent hypokalemia, significant bradycardia, acute myocardial ischemia, clinically relevant heart failure with reduced left ventricular ejection fraction, or history of symptomatic arrhythmia.
5. If they experience heart palpitations or fainting episodes after receiving gadobutrol injection, please contact the physician.
6. Please inform their physician if they are or plan to become pregnant or breastfeeding.
7. Inform the physician of any medications being used.

Epilepsy

Like with other gadolinium containing contrast agents special precaution is necessary in patients with a low threshold for seizures.

[Use in Pregnant and Lactating Women]

Pregnancy

There are no adequate data from the use of gadobutrol injection in pregnant women.
The results of repeated dosing studies of clinically relevant doses in animal experiments are shown in [Pharmacology and Toxicology].
The potential risk of single administration for humans is unknown.
Gadobutrol injection should not be used during pregnancy unless clearly necessary.

Lactation

Very small amounts of gadolinium-containing contrast agents can enter the milk. Breast feeding should be discontinued for at least 24 hours after the administration of gadobutrol.
Preclinical data show that gadobutrol is excreted into breast milk in very small amounts (less than 0.1% of the dose intravenously administered), and the absorption via the gastrointestinal tract is poor (approximately 5% of the dose orally administered was excreted in the urine) (see [Pharmacokinetics]).
At clinical doses, this product is not expected to affect the baby. This product can also be used during lactation.

[Pediatric Use]

For children who have not received an electrocardiogram, the possibility of congenital long QT syndrome must be ruled out before administration of gadobutrol injection.
For the above indications, the recommended dose for children and adolescents aged 2 years and older is 0.1 mmol gadobutrol injection/kg body weight (equivalent to 0.1ml/kg body weight).
For children and adolescents, doses > 0.1 ml/kg body weight should not be given.
Due to the lack of effectiveness and safety data, gadobutrol injection is not recommended for patients under 2 years of age.

[Geriatric Use]

Because the elderly may have the problem of impaired renal clearance of gadobutrol, special attention should be paid to screening for kidney dysfunction in patients over 65 years of age.

[Drug Interactions]

No interaction studies have been performed.

[Overdose]

A single daily dose of 1.5 mmol gadobutrol/kg body weight can be well tolerated.

In clinical applications, no poisoning reaction caused by drug overdose has been reported so far.

Due to the potential effect of gadobutrol injection overdosage on repolarization of the heart, it may interfere with the heart rhythm. In the event of overdose, cardiovascular monitoring (including electrocardiogram) and preventive measures for renal function control are recommended.

Gadobutrol can be eliminated by extracorporeal dialysis (see [Precautions]).

[Clinical Trials]

Central nervous system imaging

Seven phase III clinical studies have been conducted on gadobutrol injection for craniocerebral and spinal cord imaging (including cerebral perfusion) in countries including China. A total of 928 patients were enrolled in these studies. The purpose of effectiveness assessment in these clinical studies was to confirm that the brain and spinal cord lesions after intravenous administration of gadobutrol injection produced sufficient signal enhancement on T1-weighted images and sufficient signal loss on cerebral perfusion T2* weighted images. In all studies, the images were compared with MRI plain scans. In most of the studies, the product was compared with extracellular magnetic resonance contrast agents that had been approved for marketing.

Effectiveness data of pivotal phase III clinical studies abroad

Imaging technical indicators: At different concentrations of gadobutrol, the T1-weighted image signals of the brain and spinal cord lesions were enhanced in most patients after the contrast agent was injected, and the increases in signal-to-noise ratio and contrast-to-noise ratio of the contrast enhancement were significantly dose-dependent and had not reached saturation when the dose was up to 0.3 mmol/kg. In the brain perfusion study, the T2* rapid gradient echo (GRE) sequence was used, and the expected signal loss was observed after the injection of the contrast agent, which was significantly dose-dependent.

Ideal results could be obtained at a concentration of 1.0 mmol/ml and a dose of 0.3 mmol/kg.

Diagnostic accuracy: In all studies using conventional T1-weighted imaging, compared with plain scans, after administration of gadobutrol injection, the improvement of all parameters related to diagnostic accuracy was dose-dependent. Further information on lesion size and lesion boundaries was obtained from 46%-97% of patients after the administration of gadobutrol injection for contrast enhancement. In terms of the detection of lesions, the dose of 0.1 mmol/kg has been proved to be highly effective. In terms of lesion display, a comparison study with gadodiamide and gadoteridol confirmed that gadobutrol injection was comparably effective as gadodiamide and gadoteridol for diagnosing lesions.

Diagnostic confidence: In some studies, the diagnosis confidence was evaluated, and the results showed that compared with MRI plain scans, after the administration of 0.1 mmol/kg gadobutrol injection, the diagnosis confidence was improved in 85%-90% of patients. In the two studies to assess the diagnostic confidence, the improvement of the diagnostic confidence was assessed as “good” or “very good” in 61% and 43% of the patients after contrast enhancement with gadobutrol injection. There was no significant difference between gadobutrol injection and gadodiamide.

Effect on treatment plan: In the two studies, 15.7% and 18.2% of patients changed their treatment plans due to the results of imaging diagnosis after contrast enhancement with 0.1 mmol/kg gadobutrol injection. Further subgroup analysis showed that most of the treatment plan

changes were made based on the diagnosis after administration of the standard dose of gadobutrol injection, including spinal cord neoplasm (25%), multiple sclerosis (25%), and lesions that were non-evaluable by plain scans (34%). Among patients with primary brain tumors, 13.7% changed their treatment plans; among patients with brain metastases, 12.5% changed their treatment plans.

Effectiveness and safety for imaging of the central nervous system in Chinese patients (Report No. A40215, Study No. 309761)

This was a study comparing two extracellular magnetic resonance contrast agents in Chinese patients with known or suspected central nervous system disease—gadobutrol injection (1.0 M) and gadopentetate meglumine injection (0.5 M). The patients were randomly given a single dose of 0.1 mmol/kg body weight of gadobutrol injection or gadopentetate meglumine injection (injection volume: gadobutrol injection 0.1 ml/kg body weight, and gadopentetate meglumine injection 0.2 ml/kg body weight). The primary objective of the study was to compare the changes in the contrast-to-noise ratio (CNR, the primary effectiveness variable) before and after the use of two contrast agents, and to confirm that gadobutrol injection was not inferior to gadopentetate meglumine injection.

Table 2: Changes in the contrast-to-noise ratio (CNR) before and after contrast enhancement

Treatment group/difference	Number of patients	Mean	Standard deviation	Lower limit of the 95% confidence interval
Gadobutrol injection 0.1 ml/kg body weight	68	50.406	38.448	42.629
Gadopentetate meglumine injection 0.2 ml/kg body weight	73	43.467	39.178	35.826
Difference (gadobutrol injection - gadopentetate meglumine injection)	—	6.9389	38.828	-3.897
If the lower limit of the 95% confidence interval for the difference in the contrast-noise ratio between the two groups was on the right side of –Δ (-15%) (ie -6.52, which was equivalent to 15% of the contrast-noise ratio change (43.467) in the gadopentetate meglumine injection group), it could be confirmed that gadobutrol injection was not inferior to gadopentetate meglumine injection.				

The results of the study showed that in terms of changes in the contrast-to-noise ratio (CNR) of magnetic resonance imaging before and after contrast enhancement, gadobutrol injection was not inferior to gadopentetate meglumine injection, and it was statistically significant;
The mean change of CNR in the gadobutrol injection group was higher than that in the gadopentetate meglumine injection group. For the study's secondary effectiveness indicators (changes in the number of lesions detected after contrast enhancement, changes in diagnostic confidence, degree of lesion contrast enhancement and changes in lesion border visualization), as assessed by the investigator and 3 independent blind film-readers (blind film-readers did not know all the clinical information of the patients), various indicators were significantly improved after contrast enhancement with gadobutrol injection. The comparison with gadopentetate meglumine injection proved that gadobutrol injection was an effective contrast agent in imaging diagnosis of central nervous system lesions.

There were no deaths or serious adverse events in this study. All adverse events after study drug injection were mild. Two (2.8%) of the 71 patients given gadobutrol injection reported 4 adverse events, and 4 (5.3%) of the 75 patients given gadopentetate meglumine injection reported 4 adverse events. There was 1 adverse event in each group that was judged by the investigator to be "possibly related" to the study drug (1 case of insomnia in the gadobutrol injection group, and 1 case of erythema in the gadopentetate meglumine injection group), and other adverse events were unrelated or unlikely to be related to the study drug. From baseline to the follow-up period 20-28 hours after the contrast agent injection, one patient in the gadobutrol injection group reported clinically relevant changes in laboratory parameters (SGPT and SGOT increased; adverse events were reported, but judged to be unrelated to the study drug). No clinically significant changes in vital signs were observed in this study. During the 24-hour follow-up period, no abnormal changes were found in the physical examination compared with baseline.

Contrast-enhanced magnetic resonance angiography (CE-MRA)
Three clinical studies have been conducted abroad on gadobutrol Injection (1.0 M) in the indication of contrast enhanced magnetic resonance angiography (CE-MRA). In two Phase III clinical studies, the CE-MRA with gadobutrol injection (1.0 M) was compared with digital subtraction arterial angiography (iaDSA), the gold standard of angiography; in another clinical study, the effectiveness of gadobutrol injection and gadopentetate meglumine injection for CE-MRA was compared. A total of 466 patients were recruited in the three studies. The diagnostic effectiveness of gadobutrol injection (1.0 M) was assessed based on the assessment of the investigator and multiple independent blind film-readers (the blind film-readers did not know all clinical information of the patients).
Effectiveness data in two pivotal Phase III clinical studies
Two phase III clinical studies assessed the diagnostic efficacy of gadobutrol injection for CE-MRA by comparing with digital subtraction angiography (i.a.DSA). The primary objective of the study was to assess the coincidence rate of the two methods for the relevant clinical diagnosis of specific blood vessel segments. In one of the studies, among patients with known or suspected vascular disease in body arteries enrolled according to a pre-defined procedure, the blood vessel segments for primary effectiveness variable assessment included the common iliac or external iliac artery in 82 cases, internal carotid artery in 60 cases, aorta in 20 cases, renal artery in 10

cases, subclavian artery and mesenteric artery in 2 cases each, including almost all large blood vessels. Another study focused on peripheral arteries, including the external iliac artery or superficial femoral artery, and therefore included the most important blood vessel segments above the knee. In these two studies, based on the assessment of the investigator and all three blind film-readers, the lower limit of the 95% confidence interval of the coincidence rate of CE-MRA and DSA for specific blood vessel segments with gadobutrol injection reached statistical significance, confirming that the diagnostic efficacy of gadobutrol injection for CE-MRA for the body and peripheral arteries was equivalent to that of iaDSA.

Table 3: Primary effectiveness analysis results in the two pivotal CE-MRA clinical studies

Body artery (Study 97099)					**Peripheral artery (Study 99011)**				
Assessor	Number of cases	Coincidence rate	95% Lower limit of the confidence interval	95% Upper limit of the confidence interval	Assessor	Number of cases	Coincidence rate	Lower limit of the 95% confidence interval	Upper limit of the 95% confidence interval
Investigator	176	96.6	92.7	98.7	Investigator	186	94.1	89.7	97.0
Blind film-reader 1	173	90.2	84.7	94.2	Blind film-reader 1	178	86.0	80.0	90.7
Blind film-reader 2	171	86.6	80.5	91.3	Blind film-reader 2	179	86.6	80.7	91.2
Blind film-reader 3	174	87.9	82.1	92.4	Blind film-reader 3	181	87.9	82.2	92.2

Effectiveness and safety for CE-MRA indication in Chinese patients (Report No. A40727, Study No. 309762)

This was a randomized, controlled, crossover clinical study comparing two extracellular magnetic resonance contrast agents in Chinese patients with known or suspected arterial vascular disease in different body regions—gadobutrol injection 1.0 M (0.1 mmol/kg body weight, up to 0.3 mmol/kg body weight for multiple FOV) and gadopentetate meglumine injection 0.5 M (0.1 mmol/kg body weight, up to 0.3 mmol/kg body weight for multiple FOV). The study detected vascular stenosis and occlusive disease in three arterial areas: carotid or other aortic arch vessels (body region 1), renal arteries (body region 2), and peripheral arteries (body region 3).

The primary objective of this study was to verify that at the same dose of gadolinium administered, the diagnostic image quality (evaluated as "good" or "good") in terms of the number of blood vessel segments in different arterial and vascular regions after contrast enhancement achieved by gadobutrol injection (1.0 M) was not inferior to that of gadopentetate meglumine injection (0.5 M).

Table 4: Mean, mean ratio, and one-sided 95% confidence interval of blood vessel segments that achieved diagnostic image quality—all blood vessel segments—PPS population

	Gadopentetate meglumine injection/gadobutrol injection	Gadobutrol injection/gadopentetate meglumine injection	Mean of gadopentetate meglumine injection	Mean of gadobutrol injection	Lower limit of the one-sided 95% confidence interval	Estimated ratio (mean of gadobutrol injection/mean of gadopentetate meglumine injection)
Investigator*	35	32	8.3262	8.1066	0.9315*	0.9736
Blind film-reader 1*	34	32	8.2116	7.8338	0.9122*	0.9540
Blind film-reader 2*	34	32	7.8179	7.3942	0.8776*	0.9458
Blind film-reader 3*	34	32	5.9074	5.1381	0.7800	0.8698
Average blind film-reading 1*	34	32	7.3123	6.7887	0.8777*	0.9284
*Indicates statistical significance (one-sided 95% confidence interval greater than 0.85)						

Effectiveness for whole body lesion imaging

Effectiveness in Asian patients (Reports A51205 and A57550, Study 13297)

This was a multi-country (including China, Japan and South Korea) Phase 3 clinical study comparing parallel groups, which aimed to assess the effectiveness and safety of a single injection of gadobutrol injection (1.0 M) compared with gadopentetate meglumine injection for contrast enhanced MRI for the body/extremities (including breast, heart, abdomen, kidney, pelvic tibia or extremities) in Asian patients. A total of 178 and 185 patients received gadobutrol injection and gadopentetate meglumine injection, respectively.

The primary objective of this study was to confirm the non-inferiority of plain scan combined with an equimolar dose of gadobutrol-enhanced MRI compared with plain scan combined with 0.1 mmol/kg body weight gadopentetate meglumine for contrast enhancement in three assessment indicators—the degree of enhancement, border visualization and internal form of lesions. Together, these three evaluation indicators could be used to evaluate the ability of MRI to detect and visualize body/limb lesions.

In the gadobutrol injection and gadopentetate meglumine injection groups, the total scores (mean

± standard deviation) of the three visualization parameters of the aggregated (plain scan + enhanced) images were 9.39±1.06 and 9.34±1.23, respectively. The statistical analysis proved that gadobutrol injection was not inferior to gadopentetate meglumine injection in terms of lesion visualization.

Of the 363 patients in this study, a total of 203 Chinese patients received the study drug (100 received gadobutrol injection and 103 received gadopentetate meglumine injection). The results showed that when gadobutrol injection was assessed in the Chinese population for its ability to enhance the MRI to visualize lesions, the efficacy in this population was similar to that in Asian patients. In this subpopulation, the total scores (mean ± standard deviation) of the 3 imaging parameters of the aggregated (plain scan + enhanced) images of were 9.50±1.05 and 9.29±1.32 in the gadobutrol injection and gadopentetate meglumine injection groups, respectively. The statistical analysis proved that in the Chinese population, gadobutrol injection was not inferior to gadopentetate meglumine injection in terms of lesion visualization.

Total scores of the 3 imaging parameters of the aggregated images of gadobutrol injection and gadopentetate meglumine injection by the blind film-readers and the 95%CI for the difference between the two (PP set)

		Gadobutrol Injection	**Gadopentetate Dimeglumine Injection**	**Difference [lower limit and upper limit of the 95%CI]**
Asia	Average score by the blind film-readers	9.39±1.06 （164）	9.34±1.23 （174）	0.05±1.15 [-0.195，0.298]
China	Average score by the blind film-readers	9.50±1.05 （89）	9.29±1.32 （98）	0.22±1.20 [-0.130，0.561]

The values were presented as mean ±standard deviation (number of subjects)

The PP population (Asian study: gadobutrol injection group n=168 and gadopentetate meglumine injection group n=178, China: gadobutrol injection group n=91 and gadopentetate meglumine injection group n=100) was used for imaging assessment, but subjects without lesions (judged by all blind film-readers) were not included in the analysis.

a: Gadobutrol injection minus gadopentetate meglumine injection

Abbreviation: Cl: confidence interval

The lower limit of 95% Cl was greater than -1.2, proving that gadobutrol injection was not inferior to gadopentetate meglumine injection

References: Report A51205 and Report A57550

In Chinese patients and Asian patients, the imaging performance of gadobutrol injection was equivalent. The average score in Chinese patients was increased from 6.63 of plain scan images to 9.50 of plain + enhanced scan images (a difference of 2.85). The average score in Asian patients was increased from 6.59 of plain scan images to 9.39 of plain + enhanced scan images (a difference of 2.77).

In the Chinese population, 2 subjects (2.0%) in the gadobutrol injection group (2 adverse events) and 1 subject (1.0%) in the gadopentetate meglumine injection group (5 adverse events) reported drug-related TEAEs. In the gadobutrol injection group, the investigator reported dry mouth and proteinuria positive (reported by 1 subject each, 1.0%) as drug-related TEAEs.

In the gadopentetate meglumine injection group, the investigator reported period extrasystole, nausea, vomiting, chest discomfort, and cold sweats (reported by the same subject, 1.0%) as drug-related TEAEs.

[Pharmacology and Toxicology]

Pharmacological effects

ATC-Code：V08CA09

Mechanism of action:

Gadobutrol injection is a paramagnetic contrast agent used in magnetic resonance imaging (MRI). The contrast enhancement effect is produced by gadobutrol, which is a non-ionic compound composed of gadolinium (III) and the macrocyclic ligand dihydroxy-hydroxymethylpropyl-tetraazacyclododecane-triacetic acid (butrol).

Pharmacodynamic effects:

At clinical doses, gadobutrol leads to shortening of the relaxation times of protons in tissue water. At pH7, the magnetic field strength is 0.47T and 40℃, the relaxation rate (r1) is about 5.61/(mmol sec), as determined from the effect on spin-lattice relaxation time (T1) of the protons in the plasma; the relaxation rate (R2) is about 6.51/(mmol sec), as determined from the effect on spin-spin relaxation time (T2). The relaxivity displays only slight dependency on the strength of the magnetic field.

Gadobutrol does not cross an intact blood-brain barrier and therefore does not accumulate in healthy brain tissue or in lesions featuring an intact blood-brain barrier. With high local tissue concentrations of gadobutrol the T2 effect results in a lessening of signal intensity.

The physical and chemical constants of 1.0 mmol/ml gadobutrol injection are listed as follows:

Osmolality (37℃, mOsm/kg water)	1603
37℃ viscosity (mPa•s)	4.96

Toxicology studies

Preclinical data reveal no special hazard for humans based on conventional safety pharmacology tests, repeat-dose toxicity tests, genetic toxicity tests, and potential exposure sensitization tests.

Reproductive toxicity

Repeated intravenous administration caused a retardation of embryonal development in rats and rabbits, and an increase in embryolethality in monkeys and in rabbits at doses 8 to 16 times (based on body surface area) or 25 to 50 times (based on body weight) the diagnostic dose only. It is not known whether these effects can also be induced by a single administration.

Local tolerance and potential exposure-sensitization

In experimental local tolerance studies, single and repeated intravenous administration and single arterial administration did not cause adverse reactions. Peripheral, subcutaneous, and intramuscular administration have shown that inadvertent intravenous injection may cause mild local reactions.

Exposure-sensitization studies have not shown the potential for sensitization of this product.

Safety pharmacology

In the preclinical cardiovascular safety pharmacology studies, with the applied dose, a transient increase in blood pressure and myocardial contractility was observed.
Cardiovascular effects seen in animals (dogs) at exposure levels similar (0.25 mmol/kg) and higher (1.25 mmol/kg), respectively, to maximum clinical exposure levels were a dose dependent transient increase in blood pressure (5% and 10%, above saline control) and myocardial contractility (5% and 16%, above saline control).
Cardiovascular safety pharmacology studies as well as clinical phase I studies gave indication for a potential of gadobutrol injection to block cardiac potassium channels and an effect on cardiac repolarization when administered in doses 3 to 8-fold higher than normally administered to patients. Therefore, the possibility that gadobutrol injection may cause torsade de pointes arrhythmias in an individual patient cannot be excluded.
These effects were not observed in humans at the clinically recommended dose.

[Pharmacokinetics]
Absorption and distribution
Gadobutrol is rapidly distributed in the extracellular space. Plasma protein binding is negligible.
After a gadobutrol dose of 0.1 mmol/kg body weight, an average level of 0.59 mmol gadobutrol/L was measured in plasma 2 minutes after the injection and 0.3 mmol gadobutrol/L 60 minutes after the injection.
Metabolism
Gadobutrol is not metabolized.
Elimination
The plasma concentration of gadobutrol decreases, with a mean terminal half-life of 1.81 hours (1.33–2.13 hours).
Gadobutrol is excreted in an unchanged form via the kidneys. The extrarenal elimination is negligible.
In healthy subjects, renal clearance of gadobutrol is 1.1 to 1.7 mL/(min^{-1} ⋅ kg^{-1}) and thus comparable to the renal clearance of inulin, confirming that gadobutrol is eliminated by glomerular filtration.
Within two hours after intravenous administration more than 50% is eliminated via the urine.
Linear/non-linear
In humans, the pharmacokinetics of gadobutrol are dose-proportional (e.g., C_{max}, AUC) and dose-independent (e.g., V_{ss}, $t_{1/2}$).

[Storage]
Keep tightly sealed.

[Packaging]
Medium borosilicate glass molded vials for injection, and halogenated butyl rubber stopper for injection.
1 vial/box, 10 vials/box, 30 vials/box.

[Shelf Life] 24 months

[Executive Standard]

[**Approval number]**

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