PATIENT INFORMATION LEAFLET

GADONANS 7.5 mmol/7.5 mL solution for injection
For intravenous use.
Sterile

- ***Active substance:*** It contains 1.0 mmol gadobutrol (equivalent to 604.72 mg gadobutrol) per 1 milliliter.
  Content of 7.5 ml: 7.5 mmol gadobutrol (equivalent to 4.5354 g gadobutrol)
  Content of 15 ml: 15 mmol gadobutrol (equivalent to 9.0708 g gadobutrol)
  Content of 30 ml: 30 mmol gadobutrol (equivalent to 18.1416 g gadobutrol)

- ***Excipients:*** Calsobutrol sodium, trometamol, hydrochloric acid, water for injection.

Before you start taking this medicine, read this PATIENT INFORMATION LEAFLET carefully, because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, please ask your doctor or pharmacist.*
- *This medicine has been prescribed for you only. Do not pass it on to others.*
- *When you visit a doctor or a hospital while you are using this medicine, inform your doctor about this.*
- *Follow the instructions in this leaflet exactly. Do not use a dose above or below the dose prescribed for you.*

What Is In this Leaflet:

1. What is GADONANS and what is it used for?

- GADONANS is a contrast agent that is administered into the vein in magnetic resonance imaging only for diagnostic purposes. • Magnetic resonance imaging is obtained by viewing the behavior of water molecules in normal and abnormal tissues.
- It contains 604.72 mg active substance (gadobutrol) in 1 mL solution.
- GADONANS is presented in a colorless glass vial in packaging sizes of 7.5, 15, and 30 ml.

- GADONANS is used for magnetic resonance imaging (MRI) of the whole body in adults and children of all ages, including term infants.

2. **Before you use GADONANS**

DO NOT USE GADONANS in the following cases

- GADONANS should not be used in individuals with hypersensitivity to the active substance or its ingredients.

Use GADONANS WITH CAUTION in the following cases

- If you have marked excitement, tension and pain (which may increase the likelihood of side effects or exacerbate reactions associated with the contrast agent)
- If you have had a previous reaction to contrast agents,
- If you have or have ever had allergies (eg. hay fever, hives, etc.) or bronchial asthma
- If you have severe kidney dysfunction or acute kidney failure,
- If you previously had or are about to have a liver transplant,
- If you have severe cardiovascular disease,
- If you have a brain condition that causes seizures,
- If you have a pacemaker or any implant or clamp containing iron in your body.

Adverse effects such as redness and swelling may occur when GADONANS is injected into the veins.

The usual safety requirements for magnetic resonance imaging, particularly exclusion of ferromagnetic materials, also apply while using GADONANS.

The use of GADONANS may lead to reactions similar to allergic reactions that can cause heart problems, breathing difficulties, or skin reactions. Serious allergic reactions may occur. In general, individuals with cardiovascular disease are at higher risk of serious and even fatal consequences for severe hypersensitivity reactions. Most of these reactions occur within half an hour of administration. Therefore, monitoring is recommended after administration. Delayed reactions may occur hours or even days later (see section 4).

If you have impaired kidney function, your doctor will make sure that GADONANS has been completely eliminated from your body before giving you a second injection of GADONANS. GADONANS can be eliminated from the body via dialysis. If you have impaired kidney function, your doctor will decide whether you need dialysis after GADONANS is administered. Because renal excretion of gadobutrol may be impaired in elderly patients, it is particularly important to screen patients aged 65 and above for kidney insufficiency.

It is recommended that all patients be screened with laboratory tests for kidney dysfunction before administration of GADONANS.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of some contrast agents containing gadolinium in patients with acute or chronic severe kidney dysfunction (GFR < 30 mL/min/1.73 m²). Patients who underwent liver transplantation are at particular risk as the incidence of acute renal insufficiency is high in this population. Because NSF may occur with GADONANS in patients with severe renal insufficiency and in patients who are in the perioperative liver transplantation period, its use should be avoided unless diagnostic data are required and if these data can be obtained with non-contrast MRI.

There have been reports of a serious reaction called nephrogenic systemic fibrosis (NSF), a disease that causes thickening of the skin and connective tissues. NSF may lead to severe joint immobility and muscle weakness or cause life-threatening effects on the normal functioning of internal organs. NSF has been associated with the use of certain contrast agents containing gadolinium (including GADONANS) in patients with severe kidney insufficiency. In addition, it has been associated with the use of certain contrast agents containing gadolinium (including GADONANS) in patients with acute renal failure due to hepato-renal syndrome (kidney insufficiency in patients with advanced chronic liver failure) or in patients with acute renal failure who have recently undergone or are expected to undergo a liver transplantation. If you have any of these conditions, your doctor will administer GADONANS after serious consideration (see section 4)

Neonates and infants
GADONANS may only be used after a careful evaluation in immature infants up to 4 weeks of age and in infants younger than 1 year of age due to their immature kidney function.

Elderly patients
If you are aged 65 or above, your doctor may want you to have a blood test to check how your kidneys function before using GADONANS.

Seizure disorders
As with other contrast agents containing gadolinium, special caution is required in patients predisposed to seizures.

If these warnings are valid in your case, even for a past period, please contact your doctor.

Taking GADONANS with food and drinks
No interaction studies have been conducted.

Pregnancy
Ask your doctor or pharmacist for advice before taking this medicine.
GADONANS should not be used during pregnancy unless absolutely necessary.

If you realize that you are pregnant during your treatment, consult your doctor or pharmacist immediately.

Breastfeeding
Ask your doctor or pharmacist for advice before taking this medicine.
It is not known whether Gadobutrol passes into breast milk. You do not need to stop breastfeeding when you need an examination involving GADONANS. No effects on the infant are expected when GADONANS is used at the recommended dose. Animal studies have shown that very small amounts of the active substance (gadobutrol) pass into breast milk after administration of GADONANS, and the infant takes only a very small amount of it in breast milk. Tell your doctor if you are breastfeeding or wish to start breastfeeding. The decision on whether to continue breastfeeding 24 hours after administration of GADONANS should be made by the physician and the nursing mother.

Effects on the ability to drive and use machines
Not relevant.

Important information about certain excipients in the composition of GADONANS
GADONANS contains less than 1 mmol sodium (23 mg) per dose (based on the average amount for a person weighing 70 kg), so it can be considered essentially sodium-free.

Taking other medicines
Studies on interaction with other drugs have not been conducted.

If you are taking or have recently taken any other prescription or over-the-counter medications, please inform your doctor or pharmacist about these.

3. How to take GADONANS?
Instructions for appropriate usage and dosage/frequency of administration:
Your doctor will determine the dose of your medicine according to your body weight and the area to be examined with MR imaging and administer it to you. MR imaging should be started immediately after administration of GADONANS.

Method of administration:
GADONANS is administered intravenously. Your doctor will administer GADONANS accordingly.

Different age groups:
Use in children:
The recommended dose for children of all ages, including term infants, is 0.1 mmol gadobutrol/kg body weight (equivalent to 0.1 mL GADONANS/kg body weight) for all indications.

Use in the elderly (65 years and above):
No overall differences in safety or efficacy have been observed between the elderly (65 years and older) and younger patients in clinical studies, and other reported clinical experience has not indicated any differences in responses between elderly and younger patients. It has been concluded that no dose adjustment is necessary. It should be used with caution in elderly patients. Your doctor may order a blood test to check kidney function.

Special populations:
Liver failure: Since gadobutrol (active substance) is eliminated only by the kidneys in unchanged form, no dose adjustment is required.
Kidney failure: Your doctor will adjust the dose of your medicine according to the severity of kidney insufficiency. In addition, GADONANS should not be repeated if the injection intervals are less than 7 days.

If you feel that the effect of GADONANS is too strong or too weak, consult your doctor or pharmacist.

If you have used more GADONANS than you should:
No overdose has been reported in the use of GADONANS. In case of overdose, your doctor will administer the necessary treatment and check whether your heart and kidneys function properly. It can be removed by hemodialysis in the event of an overdose in patients with kidney insufficiency.
If you have used more GADONANS than you should, talk you your doctor or pharmacist.

If you forget to use GADONANS:
Do not take a double dose to make up for a forgotten dose.

Effects which may occur upon discontinuation of treatment wih GADONANS
GADONANS is administered only once.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects
As with all medicines GADONANS can cause side effects in individuals who are sensitive to its ingredients.

Very common:affects at least 1 in 10 patients.
Common: affects less than one in 10 patients, but more than one in 100 patients.
Uncommon: affects less than one in 100 patients, but more than one in 1000 patients.
Rare: affects less than one in 1000 patients, but more than one in 10,000 patients.
Very rare :affects less than 1 in 10,000 patients.
Unknown: Cannot be estimated from the available data.

If any of the following happens, stop taking GADONANS and tell your doctor IMMEDIATELY or go to the emergency department at your nearest hospital:

The following are uncommon but serious effects:
Hypersensitivity/allergic (anaphylactoid) reactions[ab]: (eg. severe allergy-like reaction (anaphylactoid shock)[c], circulatory collapse (shock)[c], respiratory arrest[ac], lung edema (pulmonary edema)[c], narrowing of the bronchial cavity (bronchospasm)[c], bruising (cyanosis)[c], swelling of the mouth and throat (oropharyngeal edema)[c], swelling of the larynx (laryngeal edema)[c], low blood pressure (hypotension), increased blood pressure[c], chest pain[c], rash (urticaria), swelling of the face (edema), allergic swelling of the mucous membranes, subcutaneous tissues or an internal organ (angioedema)[c], inflammation of the eye (conjunctivitis)[c], swelling of the eyelid (edema)[c], hot flashes, excessive sweating (hyperhidrosis)[c], coughing[c], sneezing[c], burning sensation[c], pallor[c], shortness of breath (dyspnea)

If you have any of these, this means you have a serious allergy to GADONANS. You may need emergency medical intervention or hospitalization. Delayed reactions have been rarely observed several hours to several days after administration of GADONANS. In such a case, contact your doctor or radiologist.

Common
- Headache
- Nausea

Uncommon
Allergy-like reactions, eg.
- Low blood pressure
- Hives
- Swelling (edema) of the face
- Swelling (edema) of the eyelids
- Facial flushing

The frequency of the following allergy-like reactions is unknown:
- Severe allergy-like reaction (anaphylactoid shock)
- Excessive drop in blood pressure (shock)
- Respiratory arrest (breathing stops)
- Accumulation of fluid in the lungs (pulmonary edema)
- Respiratory problems (bronchospasm)
- Bruised lips
- Swelling of the mouth and throat
- Swelling of the larynx
- Increased blood pressure
- Chest pain
- Swelling of the face, throat, mouth, lips and/or tongue (angioedema)
- Conjunctivitis (inflammation of the eyelid)

- Excessive sweating
- Cough
- Sneezing
- Burning in the skin and mouth
- Pale skin
- Dizziness
- Taste disturbance
- Numbness (Paraesthesia)
- Shortness of breath[a] (dyspnea)
- Vomiting
- Redness (erythema)
- Itching (including generalized itching)
- Rash (including diffuse small, flat, red spots, small, raised and circumscribed lesions, itchy rash (such as generalized macular, papular pruritic rash))
- Various administration site reactions[d] (redness, pain, etc.)
- Feeling hot

Rare

- Loss of consciousness[a]
- Convulsion
- Smell disturbance (parosmia)
- Increased heart rate (tachycardia)
- Palpitations
- Dry mouth
- Malaise
- Feeling cold

Unknown

- Cardiac arrest[a]
- Nephrogenic systemic fibrosis (NSF), a disease that mainly causes thickening of the skin and connective tissues

[a] There have been reports of life-threatening and/or fatal outcomes for this ADR (Adverse Drug Reaction).
[b] None of the symptoms under hypersensitivity/allergic reactions detected in clinical studies exceeded the frequency level of rare (except for rash)
[c] Hypersensitivity/allergic reactions detected only during post-marketing surveillance (frequency not known)
[d] Administration site reactions (of various types) include the following terms: leakage of blood and lymph fluid at the injection site (injection site extravasation), burning at the administration site, coldness at the administration site, warmth at the administration site, redness or rash at the administration site (injection site erythema), pain at the administration site, accumulation of blood at the administration site (hematoma at the injection site).

Hypersensitivity reactions develop more frequently in patients with a predisposition to allergies than in other patients. Isolated cases of NSF have been reported with GADONANS.
Fluctuations in kidney function, including elevations in serum creatinine, have been observed following administration of GADONANS.

If you notice any side effects that are not listed in this information leaflet, inform your physician or pharmacist.

Reporting of side effects
If you get any side effects, whether or not listed in this patient information leaflet, talk to your doctor, pharmacist or nurse. In addition, you can report side effects to Turkey Pharmacovigilance Center (TÜFAM) by directly clicking "Drug Side Effect Reporting" button at the web site of www.titck.gov.tr or you can call side effect reporting line at 0 800 314 00 08. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GADONANS

Keep GADONANS out of sight and reach of children in its original packaging.
Keep at room temperature below 25°C.
GADONANS remains stable for 24 hours at 20°C - 25°C after opening, and it should be discarded at the end of this period.

Use in accordance with its expiry date.

Do not use GADONANS after the expiry date which is stated on the package.

This product should be visually inspected prior to administration.
GADONANS should not be used if there is serious discoloration or particulate structure in the product. Do not use GADONANS if you notice any deterioration on the product and/or its packaging.

Do not dispose of expired or unused medicines in the household trash! Give them to the collection system established by the Ministry of Environment and Urbanization.

Marketing Authorization Holder:
Biem İlaç San. ve Tic. A.Ş.
Anıttepe Mah. Turgut Reis Cad. No: 21
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Tel: 0312 230 29 29
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Manufacturing site:
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This patient information leaflet was approved on …….

THE FOLLOWING INFORMATION IS FOR THE HEALTHCARE PROFESSIONALS ADMINISTERING THIS DRUG

Unused products or waste materials should be disposed of according to the regulations on "Control of Medical Wastes" and "Control of Packaging and Packaging Wastes". GADONANS should only be used if diagnostic data are required and cannot be obtained with non-contrast magnetic resonance imaging.

Posology/frequency and duration of administration:
It should be used at the lowest concentration that is sufficient for contrast-enhanced imaging. The dose should be calculated based on the patient's body weight and the recommended dose per kilogram specified in this section should not be exceeded.

Contrast-enhanced MRI can be started immediately after administration (shortly after injection, according to the pulse sequence and examination protocol used). Optimal signal enhancement is observed during the arterial first pass for contrast-enhanced MRA and usually in around 15 minutes following GADONANS injection in other indications, depending on the type of lesion or tissue.
T1-weighted scan sequences are particularly suitable for contrast-enhanced examinations. General safety rules such as removal of cardiac pacemaker and ferromagnetic implants should be observed in magnetic resonance imaging.

Method of administration:
GADONANS should only be administered by healthcare professionals who have experience in clinical MRI.
This product is for intravenous administration only.
This medicinal product should be visually inspected prior to use.
GADONANS should not be used in cases of severe discoloration, particulate structure or defective container.
GADONANS should only be drawn into a syringe immediately before use.

The rubber stopper should never be punctured more than once.
Any contrast agent that is not used in an examination should be discarded.
The required dose is administered as a bolus injection.
It is recommended to use syringes in brain perfusion investigations.

Adults:
Dosage depends on the indication. A single intravenous injection of 0.1 mmol gadobutrol/kg body weight (equivalent to 0.1 mL GADONANS 1.0 /kg body weight) is usually sufficient. A maximum total amount of 0.3 mmol gadobutrol/kg body weight (equivalent to 0.3 mL GADONANS 1.0/kg body weight) can be administered.

Whole body MRI (excluding MRA)
In general, administration of 0.1 mL GADONANS per kg body weight is sufficient to address the clinical question.

Additional information for cranial and spinal MRI
If clinical doubt about the lesion persists despite normal contrast-enhanced MRI, or if more information about the number, size, and extent of lesions could affect patient management or treatment, an additional 0.1 mL/kg or 0.2 mL/kg dose of GADONANS solution administered within 30 minutes following the first injection may increase the efficiency of the diagnostic examination.

Injection of 0.3 mL/kg GADONANS solution often increases the reliability of diagnosis in excluding metastases or recurrent tumors. This especially applies to lesions with poor vascularity and/or small extracellular area, or when scan sequences with relatively low T_1-weight are applied.

It is recommended to use syringes for these examinations: 0.1 – 0.3 mL/kg (3-5 mL/sec) GADONANS

CE-MRA
Imaging of a single area:
7.5 mL for a body weight less than 75 kg
10 mL for a body weight of 75 kg or above
(equivalent to 0.1 – 0.15 mmol/kg body weight)

Imaging of several areas:
15 mL for a body weight less than 75 kg
20 mL for a body weight of 75 kg or above
(equivalent to 0.2 – 0.3 mmol/kg body weight)

Additional information on special populations: Pediatric population:
The recommended dose for children of all ages, including term infants, is 0.1 mmol gadobutrol/kg body weight (equivalent to 0.1 mL GADONANS/kg body weight) for all indications.

Geriatric population (65 years and above):
No overall differences in safety or efficacy have been observed between the elderly (65 years and older) and younger patients in clinical studies, and other reported clinical experience has not indicated any differences in responses between elderly and younger patients. It has been concluded that no dose adjustment is required. It should be used with caution in elderly patients.

Liver failure:
Since Gadobutrol is eliminated only by the kidneys in unchanged form, no dose adjustment is required.

Kidney failure:
In patients with severe kidney impairment (GFR <30 mL/min/1.73 m2), GADONANS should only be used during the perioperative liver transplantation process after risk/benefit assessment, in cases where diagnostic data are required and non-contrast MRI is not suitable. If the use of GADONANS cannot be avoided, the dose should not exceed 0.1 mmol/kg body weight. Since there is limited knowledge on repeated administration, GADONANS injections should not be repeated unless the interval between injections is at least 7 days.

Contraindications
GADONANS is contraindicated in individuals with hypersensitivity to the active substance or its ingredients.

Special warnings for use
Significant excitement, anxiety, and pain may increase the risk of adverse reactions or aggravate reactions associated with the contrast agent.

Hypersensitivity
A careful risk-benefit assessment is required, particularly in patients with known hypersensitivity to GADONANS.
As with other intravenous contrast agents, GADONANS use may be associated with anaphylactoid/hypersensitivity reactions or severe idiosyncratic reactions, including shock, characterized by cardiovascular, respiratory, or cutaneous manifestations. Typically, individuals with cardiovascular disease have a higher risk of severe hypersensitivity reactions with serious and even fatal consequences.

The risk of hypersensitivity reactions is high in the following cases:
- Previous reaction to the contrast agent
- History of bronchial asthma
- History of allergic disease

The decision to use GADONANS in patients with allergic predisposition should be made after a careful consideration of the risk-benefit ratio.

Most of these reactions occur half an hour after administration.
Therefore, it is recommended to monitor the patient following the procedure.
Preparation is required for the medical treatment of hypersensitivity reactions, as well as for the establishment of emergency measures. Delayed reactions (from a few hours to several days) have been rarely observed.
Patients using beta-blockers who show such reactions may be resistant to treatment with beta-agonists.

Kidney dysfunction
No renal dysfunction has been observed to date.
All patients should be screened for kidney dysfunction by taking a history and/or laboratory tests prior to administration of GADONANS.
Since contrast agent elimination would be delayed in patients with severely impaired renal function, the benefits of the examination should be carefully considered against the risks that may be encountered in such cases.

Since Gadobutrol is excreted by the kidneys, adequate time should be allowed for the contrast agent to be eliminated from the body before re-administration in patients with renal insufficiency. Complete urinary excretion is observed within 72 hours in patients with mild to moderate renal insufficiency. At least 80% of the administered dose is excreted in the urine within 5 days in patients with severe renal insufficiency.

GADONANS can be eliminated from the body via hemodialysis. Approximately 98% of the substance is eliminated from the body after 3 dialysis sessions. In patients receiving hemodialysis during GADONANS administration, immediate initiation of hemodialysis after administration of GADONANS should be considered to enhance elimination of the contrast agent. However, there is no evidence to support initiation of hemodialysis to prevent and treat nephrogenic systemic fibrosis (NSF) in patients who do not receive hemodialysis.

It is recommended that all patients be screened with laboratory tests for kidney dysfunction before administration of GADONANS.
There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of some contrast agents containing gadolinium in patients with acute or chronic severe renal dysfunction (GFR < 30 mL/min/1.73 m²). Patients who underwent liver transplantation are at particular risk as the incidence of acute renal insufficiency is high in this population. In patients with severe renal insufficiency and in patients who are in the perioperative liver transplantation period, GADONANS use should be avoided unless diagnostic data are required and if these data can be obtained with non-contrast MRI since NSF may occur with GADONANS.

Its use should be avoided in patients with moderate renal dysfunction (GFR<30-60 mL/min/1.73 m2) due to the risk of nephrogenic systemic fibrosis (NSF).

It should not be used in patients with acute or chronic severe renal dysfunction (GFR<30 ml/min/1.73 m2), or acute renal insufficiency of any grade associated with hepato-renal syndrome or peri-operative liver transplantation period due to the risk of nephrogenic systemic fibrosis (NSF).

Elderly patients
Since the renal clearance of gadobutrol may be impaired in elderly patients, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Seizure disorders
As with other contrast agents containing gadolinium chelate, special caution is required in patients predisposed to seizures.

As with any paramagnetic contrast agent, GADONANS may reduce the visibility of lesions that are visible on non-contrast MRI. Therefore, caution should be exercised when interpreting GADONANS MRI scans without accompanying non-contrast MRI scans.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per dose (based on the average amount for a person weighing 70 kg), so it can be considered essentially sodium-free.

Pregnancy:
There has been no experience regarding the use of gadobutrol in pregnant women. Animal studies have indicated signs of reproductive toxicity at repeated high doses.
GADONANS should not be used during pregnancy unless it is clearly necessary.

Lactation:
It is not known whether GADONANS passes into breast milk. There is evidence from nonclinical studies that gadobutrol is excreted in breast milk at very low amounts (less than 0.1% of the intravenously administered dose) and that it is poorly absorbed by the gastrointestinal tract (approximately 5% of the orally administered dose was excreted in the urine). No effects on the infant are expected at clinical doses and GADONANS can be used during lactation. The decision on whether to continue breastfeeding within 24 hours after administration of GADONANS should be made by the physician or the nursing mother.

Overdose and treatment
Single doses as high as 1.5 mmol gadobutrol per body weight have been tested and tolerated well.
No indication of intoxication associated with high doses has been reported to date in clinical use. In case of inadvertent overdose, cardiovascular monitoring (including ECG) and renal function check are recommended as a precaution.

GADONANS can be eliminated via hemodialysis.

GADONANS can be eliminated by hemodialysis in the event of an overdose in patients with renal insufficiency. Approximately 98% of this substance is eliminated from the body after three dialysis sessions. However, there is no evidence to suggest that hemodialysis is suitable for preventing nephrogenic systemic fibrosis (NSF).

GADONANS remains stable for 24 hours at 20°C - 25°C after opening, and it should be discarded at the end of this period.

As with any paramagnetic contrast agent, GADONANS may reduce the visibility of lesions that are visible on non-contrast MRI. Therefore, caution should be exercised when interpreting GADONANS MRI scans without accompanying non-contrast MRI scans.