

## Important Update - Availability of Bayer's MRI (Magnetic Resonance Imaging) Contrast agents

Certain batches of pharmaceutical products from our company's Supply Center in Berlin where final formulation and packaging of Bayer's Magnetic Resonance Imaging (MRI) Contrast agents occur have recently been on hold due to a technical problem. This production stoppage has caused a near-term impact on the fulfillment of Bayer's MRI contrast agents. The technical issue has been resolved and production has resumed.

**Please Note: There is no risk to patients associated with this issue. None of the impacted product was released. All available product on the market passed Bayer's comprehensive quality assurance measures and safety standards.**

We are actively working to find ways to increase production, including adding additional production capacity. However, there will be intermittent product shortages over the next several months. Bayer regrets any inconvenience this may cause for our customers, patients and users of our products.

### Background on Technical Issue

A defect was found in the equipment used to clean the system at the Manufacturing site, leading to the shutdown of our Berlin Production capabilities. This is impacting production schedules resulting in intermittent product supply shortages.

### US Products impacted

At this point in time, certain presentations of MRI contrast will be affected. These include:

Product	Description	NDC Number
<b>Gadavist®</b> (gadobutrol) injection 1mmol/mL	7.5 mL vial 10 mL vial 30 mL vial (PBP)	50419-325-11 50419-325-12 50419-325-14
<b>Eovist®</b> (gadoxetate disodium) injection 0.25mmol/mL	15 mL vial	50419-320-15
<b>Magnevist®</b> (gadopentetate dimeglumine) injection 0.5mmol/mL	20 mL vial	50419-188-84

### Safety Assurance – Customer Supply

The impacted batches were successfully identified through our quality control processes and blocked from release. All product inventories currently in the market are safe for patient use.

### Clarifying Information Regarding FDA Action

The FDA has been notified of our MRI contrast supply situation. We will keep the FDA and customers informed on ongoing developments.

### Patient Impact

Bayer is working closely with wholesalers and customers to help ensure contrast availability so that patient procedures are not affected. We are strongly committed to patient safety and care. Bayer is doing everything possible to rectify the situation and ensure patients' contrast needs are met.

**Please see Important Safety Information, including Boxed Warnings for Gadavist (gadobutrol) injection, Eovist (gadoxetate disodium) injection and Magnevist (gadopentetate dimeglumine) injection on the following pages.**

## **INDICATIONS and IMPORTANT SAFETY INFORMATION**

### **INDICATIONS AND USAGE: MAGNEVIST® (gadopentetate dimeglumine) Injection**

**Central Nervous System:** Magnevist® (gadopentetate dimeglumine) injection is indicated for the use with magnetic resonance imaging (MRI) in adults and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues. Magnevist® has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

**Extracranial/Extraspinal Tissues:** Magnevist® is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the head and neck.

**Body:** Magnevist® is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the body.

### **IMPORTANT SAFETY INFORMATION FOR MAGNEVIST**

#### **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 may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- Do not administer MAGNEVIST to patients with:
  - Chronic, severe kidney disease (GFR <30 mL/min/1.73m<sup>2</sup>), or
  - Acute kidney injury
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.

Do not exceed the recommended MAGNEVIST dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration.

**Contraindications:** Magnevist® is contraindicated in patients with:

- Chronic, severe kidney disease (glomerular filtration rate, GFR <30 mL/min/1.73m<sup>2</sup>), or
- Acute kidney injury, or
- History of severe hypersensitivity reactions to Magnevist®.

**Hypersensitivity Reactions:** Anaphylactoid and anaphylactic reactions with cardiovascular, respiratory and/or cutaneous manifestations rarely resulting in death have occurred. The risk of hypersensitivity reactions is higher in patients with a history of reaction to contrast media, bronchial asthma, or allergic disorders. Hypersensitivity reactions can occur with or without prior exposure to GBCAs.

**Renal Failure:** In patients with renal impairment, acute renal failure (acute kidney injury) requiring dialysis or worsening renal function has occurred, mostly within 48 hours of Magnevist® Injection. The risk of acute renal failure is higher with increasing dose of contrast. Use the lowest possible dose, evaluate renal function in patients with renal impairment, and allow sufficient time for contrast elimination before re-administration. Elimination half-life in patients with mild or moderate renal impairment is 3 to 4 hours. Elimination half-life in patients with severe renal impairment is about 11 hours. Magnevist® is cleared by glomerular filtration and is dialyzable. After 3 dialysis sessions of 3 hours each, about 97% of the administered dose is eliminated from the body; each dialysis session removes about 70% of the circulating drug.

**Please see additional Important Safety Information for Magnevist (gadopentetate dimeglumine) (continued on the next page)**

## **Important Safety Information for Magnevist (gadopentetate dimeglumine)**

*(continued)*

**Injection Site Reaction:** Skin and soft tissue necrosis, thrombosis, fasciitis, and compartment syndrome requiring surgical intervention (e.g., compartment release or amputation) have occurred very rarely at the site of the contrast injection or the dosed limb. Total volume and rate of Magnevist® Injection, extravasation of contrast agent, and patient susceptibility might contribute to these reactions. Phlebitis and thrombophlebitis may be observed generally within 24 hours after Magnevist® Injection and resolve with supportive treatment. Determine the patency and integrity of the intravenous line before administration of Magnevist® Injection. Assessment of the dosed limb for the development of injection site reactions is recommended.

**Interference with Visualization of Lesions with Non-Contrast MRI:** As with any paramagnetic contrast agent, Magnevist® Injection might impair the visualization of lesions seen on non-contrast MRI. Therefore, caution should be exercised when Magnevist® MRI scans are interpreted without a companion non-contrast MRI scan.

**Adverse Reactions:** In clinical trials, the most frequently reported adverse reactions ( $\geq 1\%$ ) included headache (4.8%), nausea (2.7%), injection site coldness/localized coldness (2.3%) and dizziness (1%).

Please see [Magnevist Full Prescribing Information](#)

## **INDICATIONS AND USAGE: GADAVIST® (gadobutrol) Injection**

Gadavist® (gadobutrol) injection is a gadolinium-based contrast agent indicated for use with magnetic resonance imaging (MRI):

- To detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system in adult and pediatric patients (including term neonates)
- To assess the presence and extent of malignant breast disease

Gadavist® is indicated for use in magnetic resonance angiography (MRA):

- To evaluate known or suspected supra-aortic or renal artery disease in adult and pediatric patients (including term neonates)

## **INDICATIONS AND USAGE: EOVISt® (gadoxetate disodium) Injection**

Eovist® is indicated for intravenous use in magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in patients with known or suspected focal liver disease.

## **IMPORTANT SAFETY INFORMATION for Gadavist® (gadobutrol) and Eovist® (gadoxetate disodium)**

### **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 may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
  - chronic, severe kidney disease ( $\text{GFR} < 30 \text{ mL/min/1.73m}^2$ ), or
  - acute kidney injury
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age  $> 60$  years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

**Please see additional Important Safety Information for Gadavist (gadobutrol) and Eovist (gadoxetate disodium) *(continued on the next page)***

## **Important Safety Information for Gadavist (gadobutrol) and Eovist (gadoxetate disodium) (continued)**

### **Additional Important Safety Information for Gadavist® (gadobutrol)**

#### **Contraindication and Important Information about Hypersensitivity Reactions:**

Gadavist® is contraindicated in patients with history of severe hypersensitivity reactions to Gadavist®. Anaphylactic and other hypersensitivity reactions with cardiovascular, respiratory, or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred following Gadavist® administration. Before Gadavist® administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Gadavist®.

**Acute Kidney Injury:** In patients with chronic renal impairment, acute kidney injury sometimes requiring dialysis has been observed with the use of some GBCAs. Do not exceed the recommended dose; the risk of acute kidney injury may increase with higher than recommended doses.

**Extravasation and Injection Site Reactions:** Ensure catheter and venous patency before the injection of Gadavist®. Extravasation into tissues during Gadavist® administration may result in moderate irritation.

**Overestimation of Extent of Malignant Disease in MRI of the Breast:** Gadavist® MRI of the breast overestimated the histologically confirmed extent of malignancy in the diseased breast in up to 50% of the patients.

#### **Low Sensitivity for Significant Arterial Stenosis**

The performance of Gadavist MRA for detecting arterial segments with significant stenosis (>50% renal, >70% supra-aortic) has not been shown to exceed 55%. Therefore, a negative MRA study alone should not be used to rule out significant stenosis.

**Adverse Reactions:** The most frequent (≥0.5%) adverse reactions associated with Gadavist® in clinical studies were headache (1.5%), nausea (1.1%) and dizziness (0.5%).

Please see Full Prescribing Information for [Gadavist® \(Vials and Syringes\)](#).

Please see Full Prescribing Information for [Gadavist® \(Pharmacy Bulk Package\)](#).

### **Additional Important Safety Information for Eovist® (gadoxetate disodium)**

#### **Contraindication and Important Information about Hypersensitivity Reactions**

Eovist® is contraindicated in patients with history of severe hypersensitivity reactions to Eovist®. Anaphylactic and other hypersensitivity reactions with cardiovascular, respiratory and cutaneous manifestations, ranging from mild to severe, including shock have uncommonly occurred following Eovist® administration. Before Eovist® administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Eovist®.

#### **Acute Kidney Injury**

In patients with chronic renal impairment, acute kidney injury sometimes requiring dialysis has been observed with the use of some GBCAs. The risk of acute kidney injury might be lower with Eovist® due to its dual excretory pathways. Do not exceed the recommended dose; the risk of acute kidney injury may increase with higher than recommended doses.

#### **Extravasation and Injection Site Reactions**

Ensure catheter and venous patency before the injection of Eovist®. Extravasation into tissues during Eovist® administration may result in local tissue reactions. Strictly avoid intramuscular administration of Eovist® because it may cause myocyte necrosis and inflammation.

#### **Interference with Laboratory Tests**

Serum iron determination using complex metric methods (for example, ferrocene complexation method) may result in falsely high or low values for up to 24 hours after the examination with Eovist® because of the caloxetate trisodium excipients.

**Please see additional Important Safety Information for Eovist (gadoxetate disodium) (continued on the next page)**

## **Important Safety Information for Eovist (gadoxetate disodium) (continued)**

### **Interference with Visualization of Liver Lesions**

Severe renal or hepatic failure may impair Eovist® imaging performance. In patients with end-stage renal failure, hepatic contrast was markedly reduced and was attributed to elevated serum ferritin levels. In patients with abnormally high (>3 mg/dL) serum bilirubin, reduced hepatic contrast was observed. If Eovist® is used in these patients, complete MRI no later than 60 minutes after Eovist® administration and use a paired non-contrast and contrast MRI set for diagnosis.

**Adverse Reactions:** The most frequent ( $\geq 0.5\%$ ) adverse reactions associated with Eovist® are nausea (1.1%), headache (1.1%), feeling hot (0.8%), dizziness (0.6%), and back pain (0.6%).

Please see [Eovist Full Prescribing Information](#)