HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EOVIST® Injection safely and effectively. See full prescribing information for EOVIST Injection.

EOVIST (Gadoxetate Disodium) Injection for intravenous use

Initial U.S. Approval: 2008

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning.

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.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR < 30 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 (5.1).**

---------- RECENT MAJOR CHANGES ----------

Contraindications, Hypersensitivity (4)	10/2013
Warnings and Precautions, Acute Kidney Injury (5.3)	10/2013

----------INDICATIONS AND USAGE----------

EOVIST Injection is a gadolinium-based contrast agent indicated for intravenous use in T1-weighted magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in adults with known or suspected focal liver disease. (1)

----------DOSAGE AND ADMINISTRATION----------

The recommended dose of EOVIST is 0.1 mL/kg body weight (0.025 mmol/kg body weight) administered undiluted as a single intravenous bolus injection at a flow rate of approximately 2 mL/second. Flush the intravenous cannula with physiological saline solution after the injection. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Each mL of EOVIST Injection contains 181.43 mg gadoxetate disodium (equivalent to 0.25 mol/L gadoxetate disodium) and is available in single use vials. (3)

----------CONTRAINDICATIONS----------

EOVIST is contraindicated in patients with history of severe hypersensitivity reactions to EOVIST.

----------WARNINGS AND PRECAUTIONS----------

- Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeated dosing appears to increase the risk. (5.1)
- Hypersensitivity: anaphylactoid/hypersensitivity reactions with cardiovascular, respiratory and cutaneous manifestations, ranging from mild to severe reactions including shock can occur. Monitor patients closely for need of emergency cardiorespiratory support. (5.2)

----------ADVERSE REACTIONS----------

Adverse reactions reported in clinical studies with a frequency of 0.1% – 1% were headache, dizziness, dysgeusia, parosmia, increased blood pressure, flushing, respiratory disorders, vomiting, nausea, rash, pruritus, injection site reactions and feeling hot. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-84-BAYER (1-888-842-2937) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION:

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 (GFR < 30 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 EOVIST dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

EOVIST® Injection is a gadolinium-based contrast agent indicated for intravenous use in T_1-weighted magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in adults with known or suspected focal liver disease.

2 DOSAGE AND ADMINISTRATION

EOVIST is for intravenous administration. The recommended dose of EOVIST is 0.1 mL/kg body weight (0.025 mmol/kg body weight)

Visually inspect EOVIST for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or if particulate matter is present. EOVIST should not be mixed with other drugs. EOVIST is intended for single use, and should be used immediately after opening. The rubber stopper should never be pierced more than once.

Administer EOVIST undiluted as an intravenous bolus injection at a flow rate of approximately 2 mL/second. Flush the intravenous cannula with physiological saline solution after the injection. Discard any unused portion of an EOVIST vial.

2.1 Imaging

Liver lesions are detected and characterized with pre-contrast MR images and EOVIST MR images obtained during dynamic and hepatocyte imaging phases. During the dynamic imaging phases, use the temporal enhancement and washout pattern of intravascular EOVIST to assess lesions. Further assess lesions during a hepatocyte imaging phase, based upon the pattern of EOVIST accumulation within hepatocytes. Perform a pre-contrast MRI, inject EOVIST and begin dynamic imaging approximately 15–25 seconds after completion of the injection. Dynamic imaging consists of the arterial, the porto-venous (approximately 60 seconds post-injection), and the blood equilibrium (approximately 120 seconds) phases. Begin the hepatocyte imaging phase approximately 20 minutes post-injection. Hepatocyte phase imaging may be performed up to 120 minutes post-injection.

Elevated intrinsic levels of bilirubin (>3 mg/dL) or ferritin can reduce the hepatic contrast effect of EOVIST. Perform MR imaging no later than 60 minutes following EOVIST administration to patients with these laboratory abnormalities, including patients who have elevated ferritin levels due to hemodialysis *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.6, 8.7)]*.

Lesions with no or minimal hepatocyte function (cysts, metastases, and the majority of hepatocellular carcinomas) generally will not accumulate EOVIST. Well-differentiated hepatocellular carcinoma may contain functioning hepatocytes and can show some enhancement in the hepatocyte imaging phase. Additional clinical information is therefore needed to support a diagnosis of hepatocellular carcinoma.

3 DOSAGE FORMS AND STRENGTHS

EOVIST is a clear, colorless to pale yellow, ready-to-use aqueous solution. Each mL of EOVIST contains 181.43 mg gadoxetate disodium (equivalent to 0.25 mol/L) and is available in single use vials.

4 CONTRAINDICATIONS

EOVIST is contraindicated in patients with history of severe hypersensitivity reactions to EOVIST.

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30–59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60-89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following EOVIST administration to Bayer Healthcare (1-888-842-2937) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (for example, age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administrated to a patient. For patients at highest risk for NSF, do not exceed the recommended EOVIST dose and allow a sufficient period of time for elimination of the drug prior to any re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown *[see Clinical Pharmacology (12) and Dosage and Administration (2)]*.

5.2 Hypersensitivity Reactions

Anaphylactoid and anaphylactic reactions with cardiovascular, respiratory and cutaneous manifestations, ranging from mild to severe reactions, including shock have uncommonly occurred following EOVIST administration *[see Adverse Reactions (6)]*.

- Before EOVIST administration, assess all patients for any history of a reaction to contrast media, a history of bronchial asthma and/or a history of allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to EOVIST; weigh the benefits of EOVIST MRI carefully against the risks in these clinical settings.
- Administer EOVIST only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.

Most hypersensitivity reactions to EOVIST have occurred within half an hour after administration. Delayed reactions (hours up to several days) may occur. Observe patients for signs and symptoms of hypersensitivity reactions during and following EOVIST administration. Treat these reactions with standard medications for hypersensitivity reactions.

5.3 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.

5.4 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 *[see Nonclinical Toxicology (13.2)]*.

5.5 Interference with Laboratory Tests

Serum iron determination using complexometric methods (for example, Ferrocine complexation method) may result in falsely high or low values for up to 24 hours after EOVIST administration *[see Adverse Reactions (6.1)]*.

5.6 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 MR imaging no later than 60 minutes after EOVIST administration and use a paired non-contrast and contrast MRI image set for diagnosis.

6 ADVERSE REACTIONS

The following serious but uncommon adverse reactions that have been associated with gadolinium-based contrast agents may be associated with the use of EOVIST are discussed elsewhere in the labeling:

- Nephrogenic systemic fibrosis *[see Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect EOVIST exposure in 1989 subjects who received a dose that ranged from 0.003 to 0.5 mmol/kg body weight; the majority (n=1581) received the recommended dose of 0.025 mmol/kg body weight. Overall, 59% of the subjects were men and the ethnic distribution was 64 % Caucasian, 22% Asian, 3 % Hispanic, 2% Black, and 0.5% subjects of other ethnic groups. The average age was 57.4 years (range from 19 to 84 years).

Overall, 4.3% of subjects reported one or more adverse reactions during a follow-up period that for most subjects, extended 24 hours after EOVIST administration.

The adverse reactions were predominantly of mild to moderate severity.

The most frequent (≥0.5%) adverse reactions associated with the use of EOVIST are nausea, headache, feeling hot, dizziness, and back pain.

Table 1 lists adverse reactions that occurred in ≥0.1% subjects treated with EOVIST at the recommended dose of 0.025 mmol/kg body weight.

TABLE 1: Adverse Reactions

Reaction	**Rate (%)** **n = 1581**
Nausea	1.1
Headache	1.1
Feeling hot	0.8
Dizziness	0.6
Back pain	0.6
Vomiting	0.4
Blood pressure increased	0.4
Injection site reactions (Pain, Burning, Coldness, Extravasation, Irritation)	0.4
Dysgeusia	0.4
Paresthesia	0.3
Flushing	0.3
Parosmia	0.3
Pruritus (generalized, eye)	0.3
Rash	0.3
Respiratory disorders (Dyspnea, Respiratory distress)	0.2
Fatigue	0.2
Chest pain	0.1
Vertigo	0.1
Dry mouth	0.1
Chills	0.1
Feeling abnormal	0.1

Adverse reactions that occurred with a frequency of <0.1% in subjects treated with EOVIST at the recommended dose of 0.025 mmol/kg body weight include: tremor, akathisia, bundle branch block, palpitation, oral discomfort, salivary hypersecretion, maculopapular rash, hyperhidrosis, discomfort, and malaise.

Elevation of serum iron values and serum bilirubin laboratory values were reported in less than 1% of patients after administration of EOVIST. The values did not exceed more than 2–3 times the baseline values and returned to baseline within 1 to 4 days without other signs or symptoms of other abnormalities.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported during the post-marketing use of EOVIST. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The reports were for

- Hypersensitivity/anaphylactoid reactions including shock, hypotension, pharyngolaryngeal edema, urticaria, face edema, rhinitis, conjunctivitis, abdominal pain, hypoesthesia, sneezing, cough and pallor *[see Warnings and Precautions (5.2)]*.
- Tachycardia
- Restlessness

7 DRUG INTERACTIONS

7.1 Interference with OATP Inhibitors

An interaction study in healthy subjects demonstrated that the co-administration of the OATP inhibitor erythromycin did not influence efficacy and pharmacokinetics of EOVIST. No further clinical interaction studies with other medicinal products have been performed.

7.2 Interference with Laboratory Tests

Serum iron determination

Serum iron determination using complexometric methods (for example, Ferrocine 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of EOVIST in pregnant women. While it is unknown if EOVIST crosses the human placenta, other gadolinium products do cross the placenta in humans and results in fetal exposure. Limited published human data on exposure to other gadolinium products during pregnancy did not show adverse effects in exposed neonates. Embryotoxicity occurred in pregnant rabbits that received daily gadoxetate disodium at 26 times the recommended human dose (mmol/m^2 basis), and maternal toxicity occurred in pregnant rats at doses 32 times the human dose (mmol/m^2 basis). EOVIST should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive and developmental toxicity studies were done in rats and rabbits. Gadoxetate disodium was not teratogenic when given intravenously during organogenesis to pregnant rats at doses up to 32 times the recommended single human dose (mmol/m^2 basis).

However, an increase in preimplantation loss was noted at 3.2 times the human dose (mmol/m^2 basis). Compared to untreated controls, rates of postimplantation loss and absorption increased and litter size decreased when pregnant rabbits received gadoxetate disodium at doses 26 times the recommended human single dose (mmol/m^2 basis). This occurred without evidence of maternal toxicity. Because pregnant animals received repeated daily doses of EOVIST, their overall exposure was significantly higher than that achieved with the standard single dose administered to humans.

8.3 Nursing Mothers

It is not known whether EOVIST is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when EOVIST is administered to a nursing woman. Based on pharmacokinetics of EOVIST, women with normal renal function may resume nursing with milk produced 10 hours or more following EOVIST administration with minimal risk for the presence of EOVIST within the milk.

In lactating rats given 0.1 mmol/kg [^{153}Gd] gadoxetate disodium, less than 0.5% of the total administered radioactivity was transferred to the neonates via maternal milk, mostly within 2 hours.

8.4 Pediatric Use

The safety and effectiveness of EOVIST have not been established in pediatric patients.

8.5 Geriatric Use

In clinical studies of EOVIST, 37% of the patients were 65 years of age and over, while 7% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, use of EOVIST in an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

In a clinical pharmacology study, slight to moderate differences in pharmacokinetic parameters of gadoxetate disodium (increased AUC and terminal half-life, decreased total clearance) were found in a group of geriatric volunteers in comparison to non-geriatric volunteers. No clinically relevant differences in liver contrast enhancement were found *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

In a clinical pharmacology study in groups of patients with mild or moderate hepatic impairment, a slight to moderate increase in plasma AUC, half-life and urinary excretion, as well as decrease in hepatobiliary excretion was observed in comparison to healthy subjects with normal liver function. Hepatic contrast signal did not differ among the groups.

Severe hepatic impairment may impair EOVIST imaging performance *[see Warnings and Precautions (5.6)* and *Clinical Pharmacology (12.2, 12.3)]*. In patients with severe hepatic impairment, especially in patients with abnormally high (>3 mg/dL) serum bilirubin levels, the AUC was increased up to 60% and the elimination half-life was increased up to 49%. The hepatobiliary excretion substantially decreased to about 5% of the administered dose and reduced hepatic contrast signal was observed.

A dose adjustment is not necessary for patients with hepatic impairment.

In clinical studies, 489 patients had a diagnosis of liver cirrhosis (Child-Pugh category A, n=270; category B, n=98; category C, n=24; unknown category, n=97). No difference in diagnostic performance and safety was observed among these patients.

8.7 Renal Impairment

In a clinical pharmacology study in a group of patients with moderate renal impairment, a moderate increase in AUC and terminal half-life was observed in comparison to healthy volunteers with normal renal function. Hepatic contrast did not differ among the groups.

End-stage renal failure may impair EOVIST imaging performance *[see Warnings and Precautions (5.6)* and *Clinical Pharmacology (12.2)]*. In a study of patients with end-stage renal failure, the terminal half-life was prolonged about 12-fold and the AUC was increased about 6-fold. Hepatic contrast was markedly reduced in these patients, which was attributed to significantly elevated serum ferritin levels *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2, 12.3)]*. Approximately 30% of the injected dose was removed by dialysis in a single 3-hour dialysis session, which started one hour after an EOVIST dose. EOVIST was almost completely eliminated via dialysis and biliary excretion within the observation period of 6 days, predominantly within the first 3 days.

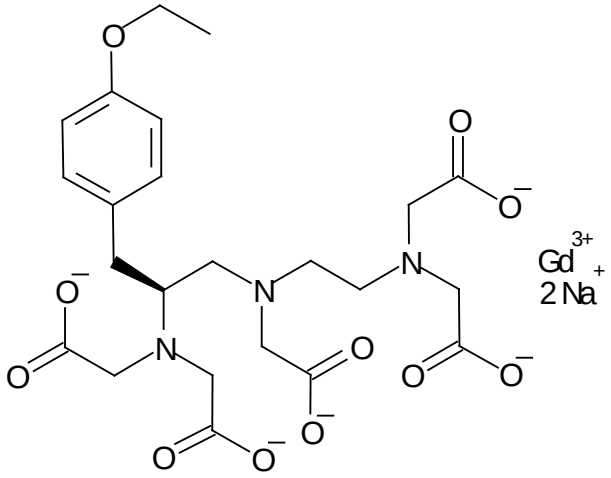
10 OVERDOSAGE

The maximum dose studied in MR imaging was 0.4 mL/kg (0.1 mmol/kg) body weight and was tolerated in a manner similar to lower doses. In clinical trials, EOVIST overdosage was not observed. In case of inadvertent overdosage in patients with severely impaired renal and/or hepatic function, EOVIST can be partially removed by hemodialysis *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

EOVIST (gadoxetate disodium) is a paramagnetic contrast agent for MRI. EOVIST is provided as a sterile, clear, colorless to pale yellow aqueous solution for intravenous injection.

EOVIST contains the active pharmaceutical ingredient gadoxetate disodium (Gd-EOB-DTPA), which is designated chemically as (4S)-4-(4-Ethoxybenzyl)-3,6,9-tris(carboxylatomethyl)-3,6,9-triazaundecanedioic acid, gadolinium complex, disodium salt with a molecular weight of 725.72 and an empirical formula of $GdC_{23}H_{28}N_3O_{11}Na_2$. The structural formula of gadoxetate disodium in aqueous solution is:



Each mL of EOVIST contains 181.43 mg of gadoxetate disodium (equivalent to 0.25 mol/L gadoxetate disodium) and the excipients caloxetate trisodium, trometamol, hydrochloric acid and/or sodium hydroxide (for pH adjustment), and water for injection. EOVIST contains no antimicrobial preservative.

EOVIST has a pH of 6.8 to 8. Pertinent physiochemical data are provided below:

TABLE 2 Physicochemical Properties

Osmolality at 37°C (Osm/kg H_2O)	0.688
Viscosity at 37°C (cP)	1.19
Density at 37°C (g/mL)	1.088

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gadoxetate disodium is a paramagnetic compound and develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by gadoxetate disodium results in a local magnetic field, yielding enhanced relaxation rates (shortening of relaxation times) of water protons in the vicinity of the paramagnetic agent, which leads to an increase in signal intensity (brightening) of blood and tissue.

In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) differences in proton density; 2) differences of the spin-lattice or longitudinal relaxation times (T_1); and 3) differences in the spin-spin or transverse relaxation time (T_2). When placed in a magnetic field, gadoxetate disodium decreases the T_1 and T_2 relaxation time in target tissue. At the recommended dose, the effect is observed with greatest sensitivity in T_1-weighted MR sequences.

12.2 Pharmacodynamics

EOB-DTPA forms a stable complex with the paramagnetic gadolinium ion with a thermodynamic stability of log KGdL=-23.46. Gadoxetate disodium is a highly water-soluble, hydrophilic compound with a lipophilic moiety, the ethoxybenzyl group (EOB). Gadoxetate disodium shows a weak (<10%), transient protein binding and the relaxivity in plasma is about 8.7 L/mmol/sec at pH 7, 39°C and 0.47 T.

Gadoxetate disodium is selectively taken up by hepatocytes *[see Clinical Pharmacology (12.3)]* resulting in increased signal intensity in liver tissue.

EOVIST exhibits a biphasic mode of action: first, distribution in the extracellular space after bolus injection and subsequently, selective uptake by hepatocytes (and biliary excretion) due to the lipophilic (EOB) moiety.

12.3 Pharmacokinetics

Distribution

After intravenous administration, the plasma concentration time profile of gadoxetate disodium is characterized by a bi-exponential decline. The total distribution volume of gadoxetate disodium at steady state is about 0.21 L/kg (extracellular space); plasma protein binding is less than 10%. Gadoxetate disodium does not pass the intact blood-brain barrier and diffuses through the placental barrier *[see Nonclinical Toxicology (13.2)]*.

Elimination

Gadoxetate disodium is equally eliminated via the renal and hepatobiliary routes. The mean terminal elimination half-life of gadoxetate disodium (0.01 to 0.1 mmol/kg) has been observed in healthy volunteers of 22–39 years of age to be 0.91 to 0.95 hour. Clearance appeared to decrease slightly with increasing age. The pharmacokinetics are dose-linear up to a dose of 0.4 mL/kg (0.1

mmol/kg), which is 4 times the recommended dose *[see Use in Specific Populations (8.5, 8.6,* and *8.7)]*.

A total serum clearance (Cl_{tot}) was 250 mL/min, whereas the renal clearance (Cl_r) corresponds to about 120 mL/min, a value similar to the glomerular filtration rate in healthy subjects.

Metabolism

Gadoxetate disodium is not metabolized.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies of EOVIST have been conducted.

Gadoxetate disodium was not mutagenic in *in vitro* reverse mutation tests in bacteria, or in chromosome aberration tests in human peripheral blood lymphocytes, and was negative in an *in vivo* micronucleus test in mice after intravenous injection of doses up to 4 mmol/kg.

Gadoxetate disodium had no effect on fertility and general reproductive performance of male and female rats when given in doses 6.5 times the human dose (based on body surface area).

13.2 Animal Toxicology and/or Pharmacology

A dose-related increase in QTc which was resolved by 30 minutes post dosing was observed in dogs when given a single dose of EOVIST. The increase was noted when given in doses equal to or greater than 0.1 mmol/kg (2.2 times the human dose). Maximum increase in QTcF was equal to or less than 20 ms at doses up to 0.5 mmol/kg (11 times the human dose).

A gait disturbance was observed in 1 of 3 mice when given EOVIST at a dose of approximately 1.1 mmol/kg (3.6 times the human dose); the disturbance occurred at 30 minutes post dosing and resolved at 4 hours post dosing.

Local intolerance reactions, including moderate interstitial hemorrhage, edema, and focal muscle fiber necrosis, were observed after intramuscular administration of EOVIST *[see Warning and Precautions (5.4)]*.

14 CLINICAL STUDIES

Patients with suspected or known focal liver lesions were enrolled in two of four non-randomized, intrapatient-controlled studies that evaluated predominantly the detection (studies 1 and 2) or morphological characterization (studies 3 and 4) of liver lesions. Studies 1 and 2 ("detection" studies) enrolled patients who were scheduled for liver surgery. MRI results were compared to a reference standard that consisted of surgical histopathology and the results from intra-operative ultrasound of the liver. The studies assessed the sensitivity of pre-contrast MRI and EOVIST-contrasted MRI for the detection of liver lesions, when each set of images was compared to the reference.

Studies 3 and 4 ("characterization" studies) enrolled patients with known or suspected focal liver lesions, including patients who were not scheduled for liver surgery. MRI results were compared to a reference standard that consisted of surgical histopathology and other prospectively defined criteria. The studies assessed the correctness of liver lesion characterization by pre-contrast MRI and EOVIST-contrasted MRI, when each set of images was compared to the reference. Lesions were characterized as one of the following choices: hepatocellular carcinoma, cholangiocarcinoma, metastasis, focal lymphoma, adenoma, focal nodular hyperplasia, hemangioma, abscess, focal liver fibrosis, regenerative nodule, focal fat, hydatid cyst, liver cyst, "not assessable", normal, no lesion or "other."

In all four studies, patients underwent a baseline, pre-contrast MRI followed by the administration of EOVIST at a dose of 0.025 mmol/kg, with MRI performed immediately (the "dynamic" phase) and at 10 to 20 minutes following EOVIST administration (the "hepatocyte" phase). Patients also underwent computerized tomography with contrast examinations of the liver. Pre-contrast MRI and EOVIST-contrasted MR images were evaluated in a systematic, randomized, paired and unpaired fashion by three radiologists who were blinded to clinical information. CT images were also evaluated by the radiologists in a separate reading session.

Diagnostic efficacy was determined in 621 patients. The average age was 57 years (range 19 to 84 years) and 54% were male. The ethnic representations were 90% Caucasian, 4% Black, 3% Hispanic, 2% Asian, and 1% of other ethnic groups.

The combination of non-contrasted and EOVIST-contrasted MR images had improved sensitivity for the detection and characterization of liver lesions, compared to pre-contrasted MR images (Tables 3 and 4). The improved sensitivity in detection of lesions was predominantly related to the detection of additional lesions among patients with multiple lesions on the pre-contrast MR images. The false positive rates for detection of lesions were similar for non-contrasted MR images and EOVIST-contrasted MR images (32% versus 34%, respectively). Liver lesion detection and characterization results were similar between CT and the combination of pre-contrasted and EOVIST-contrasted MR images.

TABLE 3 Sensitivity in Liver Lesion Detection

Diagnostic Procedure	Reader	Study 1 Sensitivity (%) n=129	Study 2 Sensitivity (%) n=126
Pre-contrast MRI	Reader 1	76	77
	Reader 2	76	73
	Reader 3	71	72
Combined pre- and EOVIST-contrast MRI	Reader 1	81	82
	Reader 2	78	76
	Reader 3	74	78
Difference: combined pre + EOVIST-contrast MRI minus pre MRI (95% confidence interval)	Reader 1	5 (1, 9)*	5 (1, 9)*
	Reader 2	2 (-1, 5)	3 (-1, 7)
	Reader 3	3 (0, 6)*	6 (0, 10)*

* Statistically significant improvement

TABLE 4 Proportion of Correctly Characterized Lesions

		Study 3		Study 4	
Diagnostic Procedure	**Reader**	**n**	**Proportion correct (%) ****	**n**	**Proportion correct (%) ****

Pre-contrast MRI	Reader 1	182	51	177	60
	Reader 2	182	59	177	64
	Reader 3	182	53	177	48
Combined pre- and EOVIST-contrast MRI	Reader 1	182	67	177	61
	Reader 2	182	76	177	76
	Reader 3	182	58	177	67
Difference: combined pre- and EOVIST-contrast MRI minus pre-contrast MRI (95% confidence interval)	Reader 1		16 (7, 25)*		1 (-7, 10)
	Reader 2		17 (9, 25)*		11 (5, 18)*
	Reader 3		5 (-2, 12)		19 (11, 27)*

* statistically significant improvement

** proportion of correctly characterized lesions with respect to the reference

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Dosage Forms Supplied

EOVIST is supplied in single-dose, rubber stoppered vials containing 181.43 mg/mL of gadoxetate disodium, equivalent to 0.25 mmol/mL, in the following sizes:

10 mL single-dose vials filled with 10 mL, boxes of 5 NDC 50419-320-05

15 mL single-dose vials filled with 15 mL, boxes of 5 NDC 50419-320-15

16.2 Storage and Handling

EOVIST is a ready-to-use solution for single use only. The rubber stopper should never be pierced more than once. Unused portions should be discarded.

EOVIST should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or if particulate matter is present.

EOVIST should be used immediately after opening.

EOVIST should not be mixed with other drugs.

EOVIST should be stored at temperatures between 20–25°C (68–77°F); excursions permitted to 15–30° C *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Instruct patients receiving EOVIST to inform their physician or healthcare provider of the following:

- if they are pregnant or breast feeding
- if they have a previous history of allergic reaction to contrast media, a history of bronchial asthma or allergic respiratory disorder, or recent administration of a gadolinium based contrast agent

- if they have any history of kidney and/or liver disease
- of all medications they may be taking, including those taken without prescription

GBCAs increase the risk of NSF among patients with impaired elimination of drugs. To counsel patients at risk of NSF:

- Describe the clinical manifestation of NSF
- Describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following EOVIST administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness. Inform patients that they may experience:

- reactions along the venous injection site, such as mild and transient burning or pain or feeling of warmth or coldness at the injection site
- side effects of feeling hot, nausea, and headache

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Manufactured in Germany