

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EOVIST® 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/1.73m²), 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).

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- Recommended dose is 0.1 mL/kg body weight (2.1)
- Administer as an intravenous bolus injection (2.2)
- Follow injection with a normal saline flush (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 181.43 mg/mL in single use vials (3)

CONTRAINDICATIONS

History of severe hypersensitivity reaction to EOVIST (4)

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

Most common adverse reactions (incidence ≥ 0.5%) are nausea, headache, feeling hot, dizziness, and back pain (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.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 3/2015

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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/1.73m²), 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 EOVIIST dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration [see Warnings and Precautions (5.1)].**

1 INDICATIONS AND USAGE

EOVIIST 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of EOVIIST is 0.1 mL/kg body weight (0.025 mmol/kg body weight).

2.2 Drug Handling and Administration

- Use sterile technique when preparing and administering EOVIIST
- Visually inspect EOVIIST, supplied in a single-use vial, for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or if particulate matter is present
- Use EOVIIST immediately after obtaining appropriate dose from vial. The rubber stopper should never be pierced more than once. Discard any unused portion of an EOVIIST vial
- Administer EOVIIST undiluted as an intravenous bolus injection at a flow rate of approximately 2 mL/second
- Do not mix EOVIIST with other medications and do not administer EOVIIST in the same intravenous line simultaneously with other medications
- Flush the intravenous cannula with a normal saline solution after EOVIIST injection
- Imaging can commence immediately following EOVIIST administration

2.3 Imaging

- Liver lesions are detected and characterized with pre-contrast MRI and EOVIIST MRI obtained during dynamic and hepatocyte imaging phases. Perform a pre-contrast MRI, inject EOVIIST 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 sterile, clear, and colorless to pale yellow solution for injection containing 181.43 mg gadoxetate disodium per mL (equivalent to 0.25 mmol gadoxetate disodium per mL) supplied 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/1.73m²) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 to 59 mL/min/1.73m²) and little, if any, for patients with chronic, mild kidney disease (GFR 60 to 89 mL/min/1.73m²). 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 administered 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 [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. The usefulness of hemodialysis in the prevention of NSF is unknown.

5.2 Hypersensitivity Reactions

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

- Before EOVIIST 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 EOVIIST.
- Administer EOVIIST 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 EOVIIST have occurred within half an hour after administration. Delayed reactions can occur up to several days after EOVIIST administration. Observe patients for signs and symptoms of hypersensitivity reactions during and following EOVIIST administration.

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 EOVIIST 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.

5.4 Extravasation and Injection Site Reactions

Ensure catheter and venous patency before the injection of EOVIIST. Extravasation into tissues during EOVIIST administration may result in local tissue reactions. Strictly avoid intramuscular administration of EOVIIST 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, ferrocene complexation method) may result in falsely high or low values for up to 24 hours after the examination with EOVIIST because of the caloxetate trisodium excipients [see *Adverse Reactions* (6.1)].

5.6 Interference with Visualization of Liver Lesions

Severe renal or hepatic failure may impair EOVIIST 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 EOVIIST is used in these patients, complete MRI no later than 60 minutes after EOVIIST administration and use a paired non-contrast and contrast MRI set for diagnosis.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Nephrogenic systemic fibrosis (NSF) [see *Boxed Warning and Warnings and Precautions* (5.1)]
- Hypersensitivity reactions [see *Contraindications* (4) and *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 adverse reactions described in this section reflect EOVIIST exposure in 1,989 subjects with the majority (1,581 subjects) receiving the recommended dose. Overall, 59% of the subjects were men and the ethnic distribution was 64%

Caucasian, 22% Asian, 3% Hispanic, 2% Black, and 0.5% of subjects consisted of other ethnic groups. The average age was 57 years (age range from 19 to 84 years).

Overall, 4% of subjects reported one or more adverse reactions following EOVIIST administration. The most frequent ($\geq 0.5\%$) adverse reactions associated with the use of EOVIIST were nausea, headache, feeling hot, dizziness, and back pain. Adverse reactions were predominantly of mild to moderate severity.

Table 1 lists adverse reactions that occurred in $\geq 0.1\%$ of subjects treated with EOVIIST.

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 who received EOVIIST 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 EOVIIST. The values did not exceed more than 3 times the baseline values and returned to baseline within 1 to 4 days.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported during the postmarketing 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.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies of EOVIST in pregnant women to inform the drug-associated risk. Gadolinium-based contrast agents (GBCAs) are reported to cross the placenta and limited published data do not report adverse effects in neonates who were exposed to GBCAs in-utero. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies. No teratogenicity was observed with repeated daily intravenous administration of gadoxetate disodium to rats during organogenesis at doses up to 32 times the recommended single human dose; however, an increase in preimplantation loss was noted at doses 3.2 times the single human dose. Post implantation loss was observed with repeated daily intravenous administration of gadoxetate disodium to rabbits on gestation days 6 through 18 at doses 26 times the recommended single human dose [*see Data*]. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

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/m² basis). However, an increase in preimplantation loss was noted at 3.2 times the human dose (mmol/m² 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/m² basis). This occurred without evidence of maternal toxicity. Because pregnant animals received repeated daily doses of gadoxetate disodium, their overall exposure was significantly higher than that achieved with the standard single dose administered to humans.

8.2 Lactation

Risk Summary

There is no information regarding the presence of gadoxetate disodium in human milk, the effects of the drug in a breastfed infant, or the effects of the drug on milk production. However, published lactation data on other GBCAs report that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk and there is limited GBCA gastrointestinal absorption in the breastfed infant. In rat lactation studies with [¹⁵³Gd] gadoxetate disodium, less than 0.5% of the total administered radioactivity was transferred to the nursing pup.

Clinical Considerations

A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for up to 10 hours after EOVIST administration in order to minimize exposure to a breastfed infant.

Data

Animal Data

In lactating rats given 0.1 mmol/kg [¹⁵³Gd] 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

Adequate and well-controlled studies of EOVIIST in pediatric patients have not been conducted. An observational study with EOVIIST was performed in 52 patients (aged > 2 months and < 18 years) referred for evaluation of suspected or known focal liver lesions. EOVIIST improved border delineation and increased contrast of the primary lesion in the majority of patients when compared to non-contrast images. No safety issues were identified.

No dose adjustment according to age is necessary in pediatric patients. The safety and effectiveness of EOVIIST have not been established in premature infants.

NSF Risk

No case of NSF associated with EOVIIST or any other GBCA has been identified in pediatric patients ages 6 years and younger.

Juvenile Animal Data

Single and repeat-dose toxicity studies in neonatal and juvenile rats did not reveal findings suggestive of a specific risk for use in pediatric patients including term neonates and infants.

8.5 Geriatric Use

In clinical studies of EOVIIST, 674 (34%) patients were 65 years of age and over, while 20 (1%) were 80 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 EOVIIST 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.

8.6 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 EOVIIST imaging performance [see *Warnings and Precautions (5.6)*]. 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)*]. Approximately 30% of the injected dose was removed by dialysis in a single 3-hour dialysis session, which started one hour after an EOVIIST dose. EOVIIST was almost completely eliminated via dialysis and biliary excretion within the observation period of 6 days, predominantly within the first 3 days.

8.7 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 EOVIIST imaging performance [see *Warnings and Precautions (5.6)*]. 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.

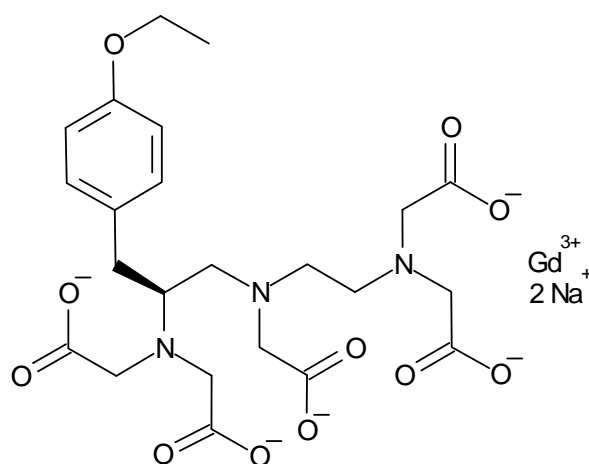
10 OVERDOSAGE

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 case of inadvertent overdosage in patients with severely impaired renal and/or hepatic function, EOVIIST can be partially removed by hemodialysis [see *Use in Specific Populations (8.6)*].

11 DESCRIPTION

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

EOVIIST contains the active pharmaceutical ingredient, gadoxetate disodium (Gd-EOB-DTPA). The chemical name for gadoxetate disodium is (4S)-4-(4-Ethoxybenzyl)-3,6,9-tris(carboxylatomethyl)-3,6,9-triazaundecanedioic acid, gadolinium complex, disodium salt. Gadoxetate disodium has 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 EOVIIST contains 181.43 mg of gadoxetate disodium (equivalent to 0.25 mmol/mL gadoxetate disodium) and the excipients caloxetate trisodium, trometamol, hydrochloric acid and/or sodium hydroxide (for pH adjustment), and water for injection. EOVIIST contains no antimicrobial preservative.

Pertinent physiochemical properties of EOVIIST are provided in Table 2.

Table 2 Physicochemical Properties

Osmolality at 37°C (Osm/kg H ₂ O)	0.688
Viscosity at 37°C (cP)	1.19
Density at 37°C (g/mL)	1.088
pH	6.8-8

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 $\log K_{GdL} = -23.46$. 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 [*see Dosage and Administration (2.3)*].

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 penetrate the intact blood-brain barrier and it does diffuse 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 (8.4, 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 EOVIIST 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 EOVIIST. 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 EOVIIST 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 EOVIIST [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, inpatient-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 EOVIIST-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 EOVIIST-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 EOVIIST at a dose of 0.025 mmol/kg, with MRI performed immediately (the "dynamic" phase) and at 10 to 20 minutes following EOVIIST administration (the "hepatocyte" phase). Patients also underwent computerized tomography with contrast examinations of the liver. Pre-contrast MRI and EOVIIST-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 EOVIIST-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 EOVIIST-contrasted MR images (32% versus 34%, respectively). Liver lesion detection and characterization results were similar between CT and the combination of pre-contrasted and EOVIIST-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

Diagnostic Procedure	Reader	Study 3		Study 4	
		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 How Supplied

EOVIST is supplied in single-dose, rubber stoppered vials containing 181.43 mg/mL of gadoxetate disodium (equivalent to 0.25 mmol/mL gadoxetate disodium), 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

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

EOVIST is a ready-to-use solution for single use only. Visually inspect EOVIIST for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or if particulate matter is present. The rubber stopper should not be pierced more than once. Use EOVIIST immediately after opening. Unused portions should be discarded.

17 PATIENT COUNSELING INFORMATION

Nephrogenic Systemic Fibrosis

Instruct patients to inform their physician if they:

- Have a history of kidney disease and/or liver disease
- Have recently received a GBCA

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 EOVIIST 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.

Common Adverse Reactions

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 headache, nausea, abnormal taste and feeling hot

General Precautions

Instruct patients receiving EOVIIST to inform their physician if they:

- Are pregnant or breastfeeding
- Have a history of allergic reaction to contrast media, bronchial asthma or allergic respiratory disorder

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