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 is not available with non-contrast enhanced MRI or other modality.

• 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 (e.g. age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1).

Dosage and Administration

Administer ABLAVAR injection by an intravenous bolus, manually or by power injection, at a dose of 0.12 mg/kg body weight (0.03 mmol/kg) over a period of time up to 30 seconds followed by a 25-30 mL normal saline flush. (2.1) Imaging is performed in two stages, the dynamic stage which begins immediately following ABLAVAR injection and the steady-state stage which begins following dynamic imaging; generally 5 to 7 minutes after ABLAVAR Injection. (2.2)

DOSAGE FORMS AND STRENGTHS

Each mL of ABLAVAR Injection contains gadofosveset trisodium (equivalent to 0.25 mmol/mL) and is available in single-use vials (3).

CONTRAINDICATIONS

• History of a prior allergic reaction to a gadolinium-based contrast agent (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 reactions, including anaphylactoid and/or anaphylactic reactions may result from ABLAVAR administration. Assess patients for a history of allergic reactions to gadolinium-based contrast agents and monitor patients closely for need of emergency cardiopulmonary support (5.2).
• Gadolinium-based contrast agents, including ABLAVAR may increase the risk for acute renal failure in patients with a history of renal insufficiency (5.3).
• GcI prolongation has been reported following ABLAVAR administration. Assess patients for a history of underlying conditions that may predispose to arrhythmias due to GcI prolongation (5.4).

ADVERSE REACTIONS

The most common (>2%) adverse reactions are pruritus, headache, nausea, vasodilatation, and paresthesia (6.1, 6.2).

WARNING: Nephrogenic Systemic Fibrosis

1. INDICATIONS AND USAGE

ABLAVAR is indicated for use as a contrast agent in magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease. (1)

2. DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

Administer ABLAVAR as an intravenous bolus injection, manually or by power injection, at a dose of 0.12 mg/kg body weight (0.03 mmol/kg) over a period of time up to 30 seconds followed by a 25-30 mL normal saline flush. (2.1) Imaging is performed in two stages, the dynamic stage which begins immediately following ABLAVAR injection and the steady-state stage which begins following dynamic imaging; generally 5 to 7 minutes after ABLAVAR Injection. (2.2)

Table 1. Weight-Adjusted Volumes for the 0.03 mmol/kg Dose

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Volumes (mL)</th>
<th>Weight-Adjusted Volumes (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>88</td>
<td>2.2</td>
</tr>
<tr>
<td>50</td>
<td>110</td>
<td>2.2</td>
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<tr>
<td>60</td>
<td>132</td>
<td>2.2</td>
</tr>
<tr>
<td>70</td>
<td>154</td>
<td>2.2</td>
</tr>
<tr>
<td>80</td>
<td>176</td>
<td>2.2</td>
</tr>
<tr>
<td>90</td>
<td>198</td>
<td>2.2</td>
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<td>130</td>
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<td>330</td>
<td>2.2</td>
</tr>
<tr>
<td>160</td>
<td>352</td>
<td>2.2</td>
</tr>
</tbody>
</table>

2.2 Imaging Guidelines

ABLAVAR imaging is completed in two stages: the dynamic imaging stage and the steady-state imaging stage. Both stages are essential for adequate imaging and not available with non-contrast enhanced MRI or other modalities.

To assess the initial distribution of ABLAVAR within the arterial system, begin dynamic imaging immediately upon injection. Begin steady state imaging after dynamic imaging has been completed, generally 5 to 7 minutes following ABLAVAR administration. At this time point, ABLAVAR is generally distributed throughout the blood. In clinical trials, steady-state imaging was completed in approximately one hour following ABLAVAR injection.

3. DOSAGE FORMS AND STRENGTHS

ABLAVAR Injection for intravenous use contains 244 mg/mL (0.25 mmol/mL) gadofosveset trisodium (see How Supplied/Storage and Handling (16))

4. CONTRAINDICATIONS

History of a prior allergic reaction to a gadolinium-based contrast agent.

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 in these patients unless the diagnostic information is essential and is not available with non-contrast enhanced MRI or other modality.

In clinical trials evaluating ABLAVAR with MRA, a total of 1,676 patients and 297 healthy subjects were exposed to various doses ABLAVAR. The mean age of the 1,676 patients who received ABLAVAR was 63 years (range: 18 to 95 years). 66% (1093) were men and 34% (483) were women. In this population, there were 80% (1100) Caucasian, 8% (107) Black, 12% (159) Hispanic, 1% (7) Asian, and 1% (6) patients of other racial or ethnic groups.

The following adverse reactions are discussed in greater detail in other sections of the label:

Nephrogenic Systemic Fibrosis (see Warnings and Precautions (5.1)).

In all clinical trials evaluating ABLAVAR with MRA, a total of 1,676 patients and 297 healthy subjects were exposed to various doses ABLAVAR. The mean age of the 1,676 patients who received ABLAVAR was 63 years (range: 18 to 95 years). 66% (1093) were men and 34% (483) were women. In this population, there were 80% (1100) Caucasian, 8% (107) Black, 12% (159) Hispanic, 1% (7) Asian, and 1% (6) patients of other racial or ethnic groups. The following adverse reactions occurred in ≥1% of subjects receiving ABLAVAR at a dose of 0.33 mmol/kg:
7 DRUG INTERACTIONS

Following injection, ABLAVAR binds to blood albumin and has the potential to alter the binding of other drugs that also bind to albumin. No drug interaction reactions were observed in clinical trials. Consider the possibility of ABLAVAR interaction with concomitantly administered medications that bind to albumin. An interaction may enhance or decrease the activity of the concomitant medication [see Clinical Pharmacology (12.3)].

7.1 Warfarin

In a clinical trial of 10 patients receiving a stable dose of warfarin, a single dose of ABLAVAR (0.05 mmol/kg) did not alter the anticoagulant activity of warfarin as measured by the International Normalized Ratio (INR).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of ABLAVAR in pregnant women. In animal studies, pregnant rabbits treated with gadofosveset trisodium at doses 3 times the human dose (based on body surface area) experienced higher rates of fetal loss and resorptions. Because animal reproduction studies are not always predictive of human response, only use ABLAVAR during pregnancy if the benefit to the fetus outweighs any potential risks to the fetus.

8.2 Nursing Mothers

It is not known whether gadofosveset is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ABLAVAR is administered to a woman who is breastfeeding. The risk associated with exposure ofinfants to gadolinium-based contrast agents in breast milk are unknown. Limited case reports indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in human breast milk. Studies of other gadolinium products have shown limited gastrointestinal absorption. These studies were conducted with gadolinium products with shorter half-lives than ABLAVAR. Avoid ABLAVAR administration to women who are breastfeeding unless the diagnostic information is essential and not obtainable with non-contraceptive MRA.

In animal studies, less than 1% of gadofosveset at doses up to 0.3 mmol/kg was secreted in the milk of lactating rats.

8.4 Pediatric Use

The safety and effectiveness of ABLAVAR in patients under 18 years of age have not been established. The risks associated with ABLAVAR administration to pediatric patients are unknown and insufficient data are available to establish a dose. Because ABLAVAR is eliminated predominantly by the kidneys, pediatric patients with immature renal function may be at particular risk for adverse reactions.

8.5 Geriatric Use

In clinical trials, no overall differences in safety and efficacy were observed between geriatric patients ≥ 65 years of age and younger patients. However, clinical experience has not identified differences in responses between elderly and younger patients, greater susceptibility to adverse effects of some older individuals cannot be ruled out.

10 OVERDOSAGE

An injection of ABLAVAR has been administered to humans up to a dose of 0.15 mmol/kg (5 times the clinical dose). No ABLAVAR overdoses were reported in clinical trials. In the event of an overdose, direct treatment toward the removal of excess gadofosveset is recommended. Elimination of the total administered dose of gadolinium in urine is achieved 16.3 ± 2.6 hours. The mean total clearance of gadofosveset is 6.57 ± 0.97 mL/hr following the administration of 0.03 mmol/kg.

Distribution The mean volume of distribution at steady state for gadofosveset was 146 ± 16 mL/kg, roughly equivalent to that of extracellular fluid. A significant portion of circulating gadofosveset is bound to plasma proteins, predominately albumin. At 0.05, 0.5, 1 and 4 hours after injection of 0.03 mmol/kg the plasma protein binding of gadofosveset ranges from 79.8 to 87.4%.

Metabolism: Gadofosveset does not undergo measurable metabolism in humans.

Excretion: Gadofosveset is eliminated primarily in the urine, with between 75% and 94% (mean of 83.7%) of an injected dose recovered in the urine. Of the total gadofosveset recovered in urine, 94% is recovered within the first 24 hours. A slight decrease in fecal elimination of gadofosveset was seen for the hepatic filter. Elimination of the total administered dose of gadolinium in humans is achieved approximately 16.3 ± 2.6 hours. The mean total clearance of gadofosveset is 6.57 ± 0.97 mL/hr following the administration of 0.03 mmol/kg.

A clinical study of gadofosveset, at a dose of 0.05 mmol/kg, was conducted in patients with mild, moderate, and severe renal impairment. The clearance decreased substantially as renal function decreased and the systemic exposure increased. The clearance of gadofosveset in patients with severe renal impairment ranged from 47% to 63% of the clearance in patients with normal renal function. The AUC in patients with moderate renal impairment was 81% of the AUC in patients with normal renal function. The AUC in patients with severe renal impairment was 72% of the AUC in patients with normal renal function.

Hemodialysis: Gadofosveset is removed from the body by hemodialysis using high flux filters. Elimination of the total administered dose of gadolinium in dialysis in 12.3 ± 8.5 hours during high-flux filter sessions using high-flux filters averaged 48.8% (9%,21%), 15% (12%,25%) for the first, second, and third sessions, respectively. Clearance of gadofosveset in patients undergoing hemodialysis was calculated as a function of increasing renal impairment (6.5× in normal subjects to 13.3× in patients with severe renal impairment).

Nephrectomy: Gadofosveset is removed from the body by hemodialysis using high flux filters. Elimination of the total administered dose of gadolinium in dialysis in 12.3 ± 8.5 hours during high-flux filter sessions using high-flux filters averaged 48.8% (9%,21%), 15% (12%,25%) for the first, second, and third sessions, respectively.

Hepatic Insufficiency: The pharmacokinetics and plasma protein binding of gadofosveset was not significantly influenced by moderate hepatic impairment. A slight decrease in fecal elimination of gadofosveset was seen for the hepatic impaired subjects (2.7%) compared to normal subjects (4.8%).

Gender: No dosage adjustment is necessary based on gender. Gender had no meaningful effect on the pharmacokinetics of gadofosveset.

Pediatric: Studies of gadofosveset in pediatric patients have not been performed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of gadofosveset. Gadofosveset was negative in the in vitro battery reverse mutation assay, CHO chromosome aberration assay, and the in vivo mouse micronucleus assay. Administration of up to 1.5 mmol/kg (9.3 times the human dose) to female rats for 2 weeks and to male rats for 4 weeks did not impair fertility [see Use in Specific Populations (8.1)].

14 CLINICAL STUDIES

Safety and efficacy of ABLAVAR were assessed in two multi-center, open-label, Phase 3 clinical trials. In both trials, patients with known or suspected peripheral vascular disease underwent MRA with and without ABLAVAR as well as catheter-based X-ray arteriography. Diagnostic efficacy was based upon reported sensitivities and specificities or area under the MRA with and without ABLAVAR, as X-ray arteriography as the reference standard.

Out of 493 patients enrolled in these two trials, 424 were included in the comparison of the diagnostic efficacy of ABLAVAR-MRA to that of non-contrast MRA in detection/exclusion of occlusive vascular disease (≥ 50% stenosis) in 7 vessel segments in each patient. Ablation of MRA images from both trials was conducted by three independent radiologist readers who were blinded to clinical data, including the results of X-ray arteriography. In these evaluations, the mean age was 67 years with a range of 29 to 87 years; 58% of the patients were over 65 years of age; 83% were white and 66% male. The primary efficacy analyses were designed to demonstrate superiority in sensitivity and non-inferiority in specificity of ABLAVAR-MRA as compared to non-contrast MRA at the vessel-segment level. The uninterpretable images were assigned an outcome of “wrong diagnosis.” Additionally, success was also based upon acceptable performance characteristics for the uninterpretable non-contrast MRA vessel segments that became interpretable following ABLAVAR administration. Specifically, the sensitivity and specificity for these ABLAVAR images were required to exceed 50%. These pre-specified success criteria were to be achieved by at least the same two readers for all primary analyses.

Sensitivity in non-inferiority and specificity was demonstrated for ABLAVAR-MRA by all three blinded readers. On average, 316 vessel segments were assessed for sensitivity and 2230 for specificity, by each reader. Table 4 summarizes the efficacy results by reader.

Among the three readers, 5 to 12% of the vessel-segments were deemed uninterpretable by non-contrast MRA. For these vessel segments, sensitivity of ABLAVAR-MRA ranged from 94% [95% CI (93%, 100%)] to 97% [95% CI (91%, 100%)] and specificity ranged from 72% [95% CI (67%,76%)] to 84% [95% CI (81%, 88%)].

16 HOW SUPPLIED/STORAGE AND HANDLING

ABLAVAR injection is a sterile, colorless, to pale yellow solution containing 244 mg/mL (0.25 mmol/mL) of gadofosveset trisodium in rubber-stoppered glass vials with an aluminum seal. ABLAVAR injection is supplied as follows:

NDC 11994-012-01 - 10 mL fills in 10 mL single use packages of 10 vials
NDC 11994-012-02 - 15 mL fills in 10 mL single use packages in packages of 10 vials

ABLAVAR injection Up to 25°C (77°F excursions permitted to 15 to 30°C [95 to 86°F]). Protect from light and freezing.

17 PATIENT COUNSELING INFORMATION

Instruct patients receiving ABLAVAR injection to inform their physician or healthcare provider if they:

• are pregnant or breast feeding
• have a history of allergic reaction to contrast media, a history of bronchial asthma or a allergic respiratory disorder
• have a history of kidney and/or liver disease
• have recently received a gadolinium-based contrast agent
• have severe heart failure or cardiac disease
• are taking any prescription or the over-the-counter medications

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

• Describe the manifestations 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 ABLAVAR 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:

• nausea or vomiting in the injection site, such as: redness, mild and transient burning or pain of feeding or warmth of the skin
• side effects of itching or nausea

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US Patents: 7,060,257; 7,729,606; 5,916,907; 6,767,929; and 7,711,815

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