



April 2011

Dear Valued Customer,

On behalf of Lantheus Medical Imaging, Inc. we would like to thank you for your interest in ABLAVAR® (gadofosveset trisodium) the only magnetic resonance angiography (MRA) contrast agent approved by the Food and Drug Administration (FDA).

ABLAVAR® is the first and only contrast agent approved for MRA evaluation of aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease.^{1,2} The albumin-binding properties of ABLAVAR® make it uniquely designed for vascular imaging allowing multiple images to be obtained using a single, low dose injection (0.03 mmol/kg) injection.^{1,3}

The addition of ABLAVAR® to the Lantheus Medical Imaging product portfolio reflects Lantheus' mission to provide pioneering medical imaging solutions to improve the treatment of human disease. Lantheus Medical Imaging will provide the service, support and expertise that our customers have come to expect with our nuclear imaging and echocardiography contrast imaging products over the past fifty years.

We are pleased to provide you with a formulary kit to help you successfully introduce ABLAVAR® to your institution. This formulary kit contains the following information:

- FDA Approval letter
- Pricing Letter
- What is ABLAVAR®
- Ordering and Contact Information
- Three clinical abstracts from pivotal Phase 2 and 3 trials
- Dosing guidelines
- ABLAVAR® full Prescribing Information

Thank you for selecting ABLAVAR®. We look forward to working with you as you introduce this first-in-class contrast imaging agent into your institution. At any time, please feel free to contact Lantheus Medical Imaging at 1-800-299-3431 for personal assistance.

References

1. ABLAVAR® [package insert]. North Billerica, MA: Lantheus Medical Imaging, Inc.; 2011.
2. U.S. Food and Drug Administration Web Site. <http://www.fda.gov/drugs>. Accessed September 28, 2009.
3. Goyen M. Gadofosveset-enhanced magnetic resonance angiography. *Vasc Health Risk Manag.* 2008;4(1):1-9.

Please see accompanying Indications, Contraindications, Important Safety Information and accompanying full Prescribing Information including boxed **WARNING** regarding Nephrogenic Systemic Fibrosis (NSF).



INDICATIONS:

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.

CONTRAINDICATIONS:

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

IMPORTANT SAFETY 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 (e.g. 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 ABLAVAR dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration.

ABLAVAR[®] Injection: As with other contrast media, the possibility of serious or life-threatening anaphylactic or anaphylactoid reactions, including cardiovascular, respiratory and/or cutaneous manifestations, should always be considered. As with other gadolinium based contrast agents, caution should be exercised in patients with renal insufficiency due to the possibility of further deterioration in renal function.

In clinical trials, a small increase (2.8 msec) in the average change from baseline in QTc was observed at 45 minutes following ABLAVAR[®] administration. These QTc prolongations were not associated with arrhythmias or symptoms. Caution should be used in patients at high risk for arrhythmias due to baseline QTc prolongation.

Have emergency resuscitative equipment available prior to and during ABLAVAR[®] administration.

Please see accompanying full Prescribing Information, including boxed **WARNING** regarding Nephrogenic Systemic Fibrosis (NSF).



NDA 21-711/S-001

SUPPLEMENT APPROVAL

Lantheus Medical Imaging
Attention: Mary E. Taylor, MPH
Vice President Global Regulatory Affairs
331 Treble Cover Road
North Billerica, MA 01862

Dear Ms. Taylor:

Please refer to your supplemental new drug application dated April 17, 2009, received April 17, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VASOVIST® (gadofosveset trisodium) Injection.

We acknowledge receipt of your submissions dated May 19, June 10, July 10 and 15, October 14 and 16, and November 11, 2009.

This "Prior Approval" supplemental new drug application provides for a change in the proprietary name of the product from VASOVIST® to Ablavar.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert). For administrative purposes, please designate this submission, "SPL for approved NDA 21-711/S-001."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on

heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDA 21-711/S-001." Approval of this submission by FDA is not required before the labeling is used.

PROPRIETARY NAME

The proposed proprietary name, Ablavar, was found acceptable on July 17, 2009.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We reiterate the postmarketing requirement for your product, as described in our approval letter of December 22, 2008. As described in that letter, you are required to conduct the following:

1. A clinical trial to collect clinical data sufficient to assess the magnitude of risk for the development of NSF (nephrogenic systemic fibrosis) with your product among patients with moderate (GFR < 60 mL/min/1.73m²) to severe renal insufficiency.

The timetable cited in our December 22, 2008, letter stated that you will conduct this clinical trial according to the following timetable:

Protocol Submission:	June, 2009
Trial Start Date:	September, 2009
Final Report Submission:	September, 2014

We acknowledge submission of the protocol to your IND on October 8, 2009 with a cross-reference letter to this NDA. Because this protocol submission date differs from that specified in timetable listed in the December 22, 2008, approval letter, we consider the status of this postmarketing requirement to be delayed, and this status has been posted on the FDA Postmarketing Requirement and Commitments website:

<http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>.

On November 11, 2009, you submitted a proposed, revised timetable that differs from the timetable listed above and cited in our December 22, 2008, letter. We remind you that an applicant's failure to comply with the approved timetable, periodic report submissions, and other requirements of section 505(o)(3)(E)(ii) will be considered a violation of that subsection unless the applicant demonstrates good cause for the noncompliance. Under section 505(o)(3)(E)(ii) of the Act, FDA will determine what constitutes good cause.

Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Rafel Rieves, M.D.
Director
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure(s)
Content of Labeling
Carton and Container Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21711	SUPPL-1	LANTHEUS MEDICAL IMAGING INC	VASOVIST(GADOFOSVESET TRISODIUM)0.25MMO1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES W MOORE
01/11/2010

RAFEL D RIEVES
01/11/2010



331 Treble Cove Road
North Billerica, MA 01862

800.362.2668
www.lantheus.com

April 12, 2011

Dear Valued Customer:

In response to your request for quotation, Lantheus Medical Imaging is pleased to quote the following:

ABLAVAR[®] (gadofosveset trisodium)

Catalog Number	Packaging Size	Price per Vial	Price Per Box*
AUST	10 mL	\$121.58	\$1,215.80
AUSF	15 mL	\$182.37	\$1,823.70

*Supplied in single use vials. Packaged 10 vials per box.

If you have any questions please contact your Sales Representative or the Lantheus Customer Service Department at 1-800-299-3431.

Thank you for your interest in Lantheus Medical Imaging, Inc.

Sincerely,

A handwritten signature in black ink that reads "Karen R. Stewich". The signature is written in a cursive style.

Karen R. Stewich
Director Sales Administration

Please see accompanying Indications, Contraindications, Important Safety Information and accompanying full Prescribing Information including boxed **WARNING** regarding Nephrogenic Systemic Fibrosis (NSF).

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 - acute kidney injury.
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ABLAVAR[®] Injection: As with other contrast media, the possibility of serious or life-threatening anaphylactic or anaphylactoid reactions, including cardiovascular, respiratory and/or cutaneous manifestations, should always be considered. As with other gadolinium based contrast agents, caution should be exercised in patients with renal insufficiency due to the possibility of further deterioration in renal function.

In clinical trials, a small increase (2.8 msec) in the average change from baseline in QTc was observed at 45 minutes following ABLAVAR[®] administration. These QTc prolongations were not associated with arrhythmias or symptoms. Caution should be used in patients at high risk for arrhythmias due to baseline QTc prolongation.

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What is ABLAVAR[®]?

ABLAVAR[®] is the first and only contrast agent approved by the FDA for MRA evaluation of aortoiliac occlusive disease in patients with known or suspected peripheral vascular disease.^{1,2}

ABLAVAR[®] is a blood-pool contrast agent that reversibly binds to albumin. This provides an expanded imaging window of up to 1 hour, which allows you to obtain bright, high-resolution steady-state images in addition to finely detailed first-pass images with a single, low-dose IV bolus of contrast agent. ABLAVAR[®] makes the MRA examination more convenient because it is less dependent on bolus dynamics.^{1,3}

And ABLAVAR[®] can be conveniently introduced into your current MRA workflow.

What is blood-pool (steady-state) imaging in MRA?

ABLAVAR[®] is the first blood-pool contrast agent specifically developed and approved for use in MRA. Engineered to reversibly bind to albumin in order to remain in the blood pool (vascular space) longer, ABLAVAR[®] also has high relaxivity, meaning spatial resolution can be increased while maintaining the same signal-to-noise ratio.³ Albumin binding decreases the relaxation time (T1) of water protons, resulting in an increased signal intensity of blood.¹

In addition to high-quality first-pass studies, the albumin binding expands your imaging window, enabling you to acquire bright, high-resolution blood-pool (steady-state) images.³

ABLAVAR[®] provided accuracy comparable to conventional X-ray angiography (XRA) and fewer uninterpretable images than XRA.^{4,5} Side effects were generally mild and transient,^{4,5} and there have been no reported cases of nephrogenic systemic fibrosis in over 90,000 patients who received gadofosveset trisodium during clinical use outside of the United States.⁶

References

1. ABLAVAR[®] [package insert]. North Billerica, MA: Lantheus Medical Imaging, Inc.; 2011.
2. U.S. Food and Drug Administration Web Site. <http://www.fda.gov/drugs>. Accessed September 28, 2009.
3. Goyen M. Gadofosveset-enhanced magnetic resonance angiography. *Vasc Health Risk Manag*. 2008;4(1):1-9.
4. Goyen M, Edelman M, Perreault P, et al. MR angiography of aortoiliac occlusive disease: a phase III study of the safety and effectiveness of the blood-pool contrast agent MS-325. *Radiology*. 2005;236(3):825-833.
5. Rapp JH, Wolff SD, Quinn SF, et al. Aortoiliac occlusive disease in patients with known or suspected peripheral vascular disease: safety and efficacy of gadofosveset-enhanced MR angiography-multicenter comparative phase III study. *Radiology*. 2005;236(1):71-78.
6. Data on file, Lantheus Medical Imaging, Inc.

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Ordering and Contact Information

Ordering ABLAVAR[®] directly from Lantheus Medical Imaging customer service:

Phone: (800) 299-3431

Fax: (978) 436-7501

Hours: Monday - Friday, 7:30 AM to 6:30 PM (EST)

Email: mics@lantheus.com

Online Ordering: <https://ecommerce.lantheus.com>

Customer return policy when ordering through Lantheus Medical Imaging customer service:

<http://www.ablavar.com/ordering-info.html>

Shipping:

ABLAVAR[®] will be shipped ambient temperature. Upon receipt, store ABLAVAR[®] up to 25°C (77° F) and protect from light and freezing.

ABLAVAR[®] will be shipped in a two day system. For overnight delivery, a \$25 handling charge will be assessed.

Item Codes

Item Code	Description	NDC
AUST	10mL fill in 10mL single use vials/ package of 10 vials	11994-0012-01
AUSF	15mL fill in 20mL single use vials/ package of 10 vials	11994-0012-02

McKesson Specialty Distributors is accepting ABLAVAR[®] orders from the following wholesalers:

Quantity	Amerisource/Bergen Order #	Cardinal Order #	McKesson Pharma Order #	SourceOne Order #	Merry X-Ray Order #
10X10mL	078-910	4275988	1767086	420702	MXR #40701010
10X15mL	078-915	4275996	1857150	420703	MXR #40701020

Customer Return Policy when ordered through any of the above listed wholesalers:

<http://www.ablavar.com/ordering-info.html>

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Additional Information

Frequently Asked Questions: <http://www.ablavar.com/faqs.html>

Material Safety Data Sheet (MSDS): <http://www.ablavar.com/prescribing.html>

Adverse Event and Product Quality Complaint Reports:

United States

Phone: (800) 343-7851

Press Option 2 for Adverse Events

Press Option 3 for Product Quality
Complaints

Fax: (866) 880-9343

Outside US/Canada

Phone: (978) 667-9531

Press Option 2 for Adverse Events

Press Option 3 for Product Quality
Complaints

Fax: (734) 929-6688

E-Mail: lantheussafety@i3drugsafety.com

Medical Information:

Phone: (800) 343-7851

Fax: (978) 671-8736

Hours: 8:30 AM to 5:00 PM Eastern Time, Monday - Friday

E-Mail: medicalinformation@lantheus.com

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The following are the clinical abstracts of the ABLAVAR[®] pivotal phase 2 and phase 3 trials:

Aortoiliac occlusive disease in patients with known or suspected peripheral vascular disease: safety and efficacy of gadofosveset-enhanced MR angiography—multicenter comparative phase III study.

Rapp JH, Wolff SD, Quinn SF, Soto JA, Meranze SG, Muluk S, Blebea J, Johnson SP, Rofsky NM, Duerinckx A, Foster GS, Kent KC, Moneta G, Middlebrook MR, Narra VR, Toombs BD, Pollak J, Yucel EK, Shamsi K, Weisskoff RM.

Radiology. 2005;236(1):71-78.

PURPOSE: To prospectively determine the safety and efficacy of the gadolinium-based blood pool magnetic resonance (MR) imaging contrast agent gadofosveset in patients known to have or suspected of having peripheral vascular disease.

MATERIALS AND METHODS: Ethical committee approval and patient written informed consent were obtained. This study was compliant with the Health Insurance Portability and Accountability Act. Adults known or suspected to have peripheral vascular disease received gadofosveset (0.03 mmol per kilogram of body weight) for MR angiography of the aortoiliac region. Gadofosveset-enhanced MR angiography and unenhanced two-dimensional time-of-flight MR angiography were compared with the reference standard, conventional angiography, for the presence of vascular stenosis. All patients were monitored for adverse events with hematologic analysis, analysis of blood chemistry, urinalysis, and electrocardiographic parameters; these methods were analyzed to determine safety.

RESULTS: A total of 274 patients were enrolled at 37 centers. Gadofosveset-enhanced MR angiography showed significant improvement ($P < .001$) compared with unenhanced MR angiography for each of the readers for diagnosis of clinically significant $\geq 50\%$ stenosis. Specificity and accuracy were significantly greater for three readers, and sensitivity increased significantly for two readers. For all readers, the area under the receiver operator characteristic curve for both quantitative and qualitative measures of significant disease increased ($P < .001$) for gadofosveset-enhanced MR angiography versus two-dimensional time-of-flight MR angiography. All readers also expressed more confidence in diagnosis ($P < .001$) and found fewer images to be uninterpretable (0.5% vs 11.0%). The most common adverse events were as follows: feeling hot, 12 (4.4%) patients; nausea, 10 (3.6%) patients; headache, nine (3.3%) patients; and burning sensation, eight (2.9%) patients. Only four serious adverse events were reported, in three patients, and all events were rated as unlikely related to the drug. No patients were excluded because of adverse events or laboratory abnormalities. There were no clinically important trends in the findings of hematologic analysis, blood chemistry, urinalysis, electrocardiography, or physical examination.

CONCLUSION: On the basis of substantial improvements over noncontrast MR angiography in efficacy and a minimal and transient side-effect profile, gadofosveset was found to be safe and effective for MR angiography in patients known or suspected to have peripheral vascular disease. © RSNA, 2005.

Link to *Radiology* to view complete paper: <http://radiology.rsna.org/content/236/1/71.long>

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MR angiography of aortoiliac occlusive disease: a phase III study of the safety and effectiveness of the blood-pool contrast agent MS-325.

Goyen M, Edelman M, Perreault P, O’Riordan E, Bertoni H, Taylor J, Siragusa D, Sharafuddin M, Mohler ER 3rd, Breger R, Yucel EK, Shamsi K, Weisskoff RM.

Radiology. 2005;236(3):825-833.

PURPOSE: To evaluate prospectively the safety and effectiveness of aortoiliac magnetic resonance (MR) angiography enhanced with MS-325 (gadofosveset trisodium) at a dose of 0.03 mmol/kg; effectiveness was defined as accuracy relative to the reference standard, conventional angiography.

MATERIALS AND METHODS: Study was approved by institutional review boards of participating institutions, and required national approvals were obtained. Study protocol conformed to Good Clinical Practice guidelines, and informed patient consent was obtained. Patients with known or suspected peripheral vascular disease received 0.03 mmol/kg MS-325 for aortoiliac MR angiography. They were also examined with conventional angiography. MS-325–enhanced MR was evaluated for safety and effectiveness. Along with unenhanced two-dimensional time-of-flight MR angiography, it was compared with conventional angiography for presence of vascular stenosis. Student *t* tests were used to identify significant improvement in diagnostic sensitivity, specificity, and accuracy, as well as quantitative characterization of stenoses by three blinded readers. Correlations between readers of conventional angiograms were calculated and compared with MR results.

RESULTS: In 174 patients, MS-325–enhanced MR angiography showed significant improvement ($P \leq .001$) in sensitivity, specificity, and accuracy for diagnosis of clinically significant ($\geq 50\%$) stenosis, compared with unenhanced MR. For all readers, areas under the receiver operating characteristic curve for both quantitative and qualitative measures of significant disease increased ($P < .001$) for MS-325–enhanced MR compared with time-of-flight MR. All readers also expressed higher confidence in diagnosis ($P < .001$) and found fewer images uninterpretable with MS-325 enhancement. All measures of interpretation accuracy approached corresponding measures of correlation between readers of conventional angiograms. Incidence of severe and serious adverse events with MS-325 was low. No patients were withdrawn from study due to adverse events or abnormalities in laboratory results. There were no clinically important trends in findings at hematology, blood chemistry, urinalysis, electrocardiography, or physical examination.

CONCLUSION: MR angiography with MS-325 provides significant improvement in effectiveness over unenhanced MR (and minimal and transient side effects) at a dose of 0.03 mmol/kg and was safe and effective for MR evaluation of patients with aortoiliac occlusive disease. © RSNA, 2005.

Link to *Radiology* to view complete paper: <http://radiology.rsna.org/content/236/3/825.long>

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MR angiography with gadofosveset trisodium for peripheral vascular disease: phase II trial.

Perreault P, Edelman MA, Baum RA, Yucel EK, Weisskoff RM, Shamsi K, Mohler ER 3rd.

***Radiology.* 2003;229(3):811-820.**

PURPOSE: To evaluate the dose response and safety of gadofosveset trisodium-enhanced magnetic resonance (MR) angiography compared with nonenhanced two-dimensional time-of-flight MR angiography and with x-ray angiography as the standard.

MATERIALS AND METHODS: In this randomized, 20-center, double-blind study, 238 men and women who had peripheral vascular disease or were suspected of having it received intravenous injection of placebo or gadofosveset (0.005, 0.01, 0.03, 0.05, or 0.07 mmol per kilogram of body weight). MR angiographic images were evaluated by three blinded readers, and x-ray angiographic images were evaluated by two readers. Hypothesis testing for the presence of a dose response was based on a linear test for trend for increase in area under the receiver operating characteristic curve as a function of dose for each reader of MR angiographic images independently.

RESULTS: Gadofosveset administration resulted in a dose-dependent increase in diagnostic accuracy for detection of aortoiliac occlusive disease as reflected in the area under the receiver operating characteristic curve for each reader ($P < .001$). The plateau in effectiveness improvement began at the 0.03 mmol/kg dose. At doses of 0.03 mmol/kg and higher, gadofosveset-enhanced MR angiography provided an approximate 20% increase in accuracy over nonenhanced MR angiography for diagnosis of clinically significant aortoiliac occlusive disease. Gadofosveset exhibited a good safety profile in all dose groups. Three serious adverse events were possibly or probably related to gadofosveset administration. There were no dose-related trends in severe or serious adverse events in patients receiving gadofosveset.

CONCLUSION: A dose of 0.03 mmol/kg of gadofosveset was safe and effective for evaluation of aortoiliac occlusive disease with MR angiography. © RSNA, 2003.

Link to *Radiology* to view complete paper: <http://radiology.rsna.org/content/229/3/811.long>

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In clinical trials, a small increase (2.8 msec) in the average change from baseline in QTc was observed at 45 minutes following ABLAVAR[®] administration. These QTc prolongations were not associated with arrhythmias or symptoms. Caution should be used in patients at high risk for arrhythmias due to baseline QTc prolongation.

Have emergency resuscitative equipment available prior to and during ABLAVAR[®] administration.

Please see accompanying full Prescribing Information, including boxed **WARNING** regarding Nephrogenic Systemic Fibrosis (NSF).



ABLAVAR[®] Dosing Guidelines¹

Administer ABLAVAR[®] as an intravenous bolus injection, manually or by power injection, at a dose of 0.12 mL/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. (See Table 1 for weight-adjusted dose volumes).

Inspect the ABLAVAR[®] vial visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present.

ABLAVAR[®] is intended for single use only and should be used immediately upon opening. Discard any unused portion of the ABLAVAR[®] vial.

Do not mix intravenous medications or parenteral nutrition solutions with ABLAVAR[®]. Do not administer any other medications in the same intravenous line simultaneously with ABLAVAR[®].

TABLE 1. Weight-Adjusted Volumes for the 0.03 mmol/kg Dose ¹		
Body Weight		Volume
Kilograms (kg)	Pounds (lb)	Milliliters (mL)
40	88	4.8
50	110	6.0
60	132	7.2
70	154	8.4
80	176	9.6
90	198	10.8
100	220	12.0
110	242	13.2
120	264	14.4
130	286	15.6
140	308	16.8
150	330	18.0
160	352	19.2

Please see accompanying Indications, Contraindications, Important Safety Information and accompanying full Prescribing Information including boxed **WARNING** regarding Nephrogenic Systemic Fibrosis (NSF).



ABLAVAR[®] Dosage Forms and Strengths¹

Each mL of ABLAVAR[®] contains 244 mg/mL gadofosveset trisodium (equivalent to 0.25 mmol/mL) and is available in 10 mL and 15 mL single use vials.

ABLAVAR[®] Imaging Guidelines¹

ABLAVAR[®] imaging is completed in 2 stages: the first-pass imaging stage and the steady-state imaging stage. Both stages are essential for adequate evaluation of the arterial system, and first-pass imaging always precedes steady-state imaging. During interpretation of the steady-state images ABLAVAR[®] within the venous system may limit or confound the detection of arterial lesions.

To assess the initial distribution of ABLAVAR[®] within the arterial system, begin first-pass imaging immediately upon injection. Begin steady-state imaging after first-pass 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 within approximately 1 hour following ABLAVAR[®] injection.

Reference

1. ABLAVAR[®] [package insert]. North Billerica, MA: Lantheus Medical Imaging, Inc.; 2011.

Please see accompanying Indications, Contraindications, Important Safety Information and accompanying full Prescribing Information including boxed **WARNING** regarding Nephrogenic Systemic Fibrosis (NSF).



INDICATIONS:

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.

CONTRAINDICATIONS:

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

IMPORTANT SAFETY 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-contrast 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 (e.g. 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 ABLAVAR dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration.

ABLAVAR[®] Injection: As with other contrast media, the possibility of serious or life-threatening anaphylactic or anaphylactoid reactions, including cardiovascular, respiratory and/or cutaneous manifestations, should always be considered. As with other gadolinium based contrast agents, caution should be exercised in patients with renal insufficiency due to the possibility of further deterioration in renal function.

In clinical trials, a small increase (2.8 msec) in the average change from baseline in QTc was observed at 45 minutes following ABLAVAR[®] administration. These QTc prolongations were not associated with arrhythmias or symptoms. Caution should be used in patients at high risk for arrhythmias due to baseline QTc prolongation.

Have emergency resuscitative equipment available prior to and during ABLAVAR[®] administration.

Please see accompanying full Prescribing Information, including boxed **WARNING** regarding Nephrogenic Systemic Fibrosis (NSF).

Ablavar®

gadofosveset trisodium

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ABLAVAR (gadofosveset trisodium) 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-contrast 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 (e.g. age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1)

RECENT MAJOR CHANGES

Boxed Warning..... 12/2010
Warnings and Precautions (5.1) 12/2010
Patient Counseling Information (17) 12/2010

INDICATIONS AND USAGE

ABLAVAR Injection is a gadolinium-based contrast agent indicated for use as a contrast agent in magnetic resonance angiography (MRA) to evaluate aortic atherosclerotic disease (AIO) in adults with known or suspected peripheral vascular disease.

DOSAGE AND ADMINISTRATION

Administer ABLAVAR Injection by an intravenous bolus, manually or by power injection, at a dose of 0.12 mL/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.

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.

DOSAGE FORMS AND STRENGTHS

Each mL of ABLAVAR Injection contains 244 mg 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 cardiorespiratory 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).
- QTc prolongation has been reported following ABLAVAR administration. Assess patients for a history of underlying conditions that may predispose to arrhythmias due to QTc prolongation (5.4).

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Lantheus Medical Imaging, Inc. at 1-978-667-9531/1-800-362-2668 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: [12/2010]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING-NEPHROGENIC SYSTEMIC FIBROSIS

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
 - Dosing Guidelines
 - Imaging Guidelines
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
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*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-contrast 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 (e.g. 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 ABLAVAR 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

ABLAVAR is indicated for use as a contrast agent in magnetic resonance angiography (MRA) to evaluate aortic atherosclerotic disease (AIO) in adults with known or suspected peripheral vascular disease [see Clinical Studies (14)].

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 mL/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. (See Table 1 for weight-adjusted dose volumes).

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

Body Weight	Volume	
	Kilograms (kg)	Pounds (lb)
40	88	4.8
50	110	6.0
60	132	7.2
70	154	8.4
80	176	9.6
90	198	10.8
100	220	12.0
110	242	13.2
120	264	14.4
130	286	15.6
140	308	16.8
150	330	18.0
160	352	19.2

Inspect the ABLAVAR vial visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present.

ABLAVAR is intended for single use only and should be used immediately upon opening. Discard any unused portion of the ABLAVAR vial.

Do not mix intravenous medications or parenteral nutrition solutions with ABLAVAR. Do not administer any other medications in the same intravenous line simultaneously with ABLAVAR.

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 evaluation of the arterial system, and dynamic imaging always precedes steady-state imaging. During interpretation of the steady-state images, ABLAVAR within the venous system may limit or confound the detection of arterial lesions.

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 within approximately one hour following ABLAVAR injection.

3 DOSAGE FORMS AND STRENGTHS

ABLAVAR is a sterile solution for intravenous injection containing 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 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 30-59 mL/min/1.73m²) and little, if any, for patients with chronic, mild kidney disease (GFR 60 – 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 ABLAVAR administration to Lantheus Medical Imaging, Inc. (1-978-667-9531)/(1-800-362-2668) or FDA (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 (e.g. 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 the 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 ABLAVAR dose and allow a sufficient period of time for elimination of the drug prior to 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

ABLAVAR may cause anaphylactoid and/or anaphylactic reactions, including life-threatening or fatal reactions. In clinical trials, anaphylactoid and/or anaphylactic reactions occurred in two of 1676 subjects. If anaphylactic or anaphylactoid reactions occur, stop ABLAVAR Injection and immediately begin appropriate therapy. Observe patients closely, particularly those with a history of drug reactions, asthma, allergy or other hypersensitivity disorders, during and up to several hours after ABLAVAR administration. Have emergency resuscitative equipment available prior to and during ABLAVAR administration.

5.3 Acute Renal Failure

In patients with renal insufficiency, acute renal failure requiring dialysis or worsening renal function have occurred with the use of other gadolinium agents. The risk of renal failure may increase with increasing dose of gadolinium contrast. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. Consider follow-up renal function assessments for patients with a history of renal dysfunction. No reports of acute renal failure were observed in clinical trials of ABLAVAR [see Clinical Pharmacology (12.3)].

5.4 QTc Prolongation and Risk for Arrhythmias

In clinical trials, a small increase (2.8 msec) in the average change from baseline in QTc was observed at 45 minutes following ABLAVAR administration; no increase was observed at 24 and 72 hours. A QTc change of 30 to 60 msec from baseline was observed in 39/702 (6%) patients at 45 min following ABLAVAR administration. At this time point, 3/702 (0.4%) patients experienced a QTc increase of >60 msec. These QTc prolongations were not associated with arrhythmias or symptoms. In patients at high risk for arrhythmias due to QTc prolongation (e.g., concomitant medications, underlying cardiac conditions) consider obtaining baseline electrocardiograms to help assess the risks for ABLAVAR administration. If ABLAVAR is administered to these patients, consider follow-up electrocardiograms and risk reduction measures (e.g., patient counseling or intensive electrocardiography monitoring) until most ABLAVAR has been eliminated from the blood. In patients with normal renal function, most ABLAVAR was eliminated from the blood by 72 hours following injection [see Clinical Pharmacology (12.3)].

6 ADVERSE REACTIONS

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

6.1 Clinical Studies Experience

Anaphylaxis and anaphylactoid reactions were the most common serious reactions observed following ABLAVAR injection administration [see Warnings and Precautions (5.2)].

In all clinical trials evaluating ABLAVAR with MRA, a total of 1,676 (1379 patients and 297 healthy subjects) were exposed to various doses ABLAVAR. The mean age of the 1379 patients who received ABLAVAR was 63 years (range 18 to 91 years); 66% (903) were men and 34% (476) 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. Table 2 shows the most common adverse reactions (≥1%) experienced by subjects receiving ABLAVAR at a dose of 0.03 mmol/kg.

Table 2 Common Adverse Reactions in 802 Subjects Receiving ABLAVAR at 0.03 mmol/kg

Preferred Term	n (%)
Pruritis	42 (5)
Headache	33 (4)
Nausea	33 (4)
Vasodilatation	26 (3)
Paresthesia	25 (3)
Injection site bruising	19 (2)
Dysgeusia	18 (2)
Burning sensation	17 (2)
Venipuncture site bruise	17 (2)
Hypertension	11 (1)
Dizziness (excluding vertigo)	8 (1)
Feeling cold	7 (1)

6.2 Post-marketing Experience

Because post-marketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The profile of adverse reactions identified during the post-marketing experience outside the United States was similar to that observed during the clinical studies experience.

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 diagnostic benefit justifies the potential risks to the fetus.

In reproductive studies, pregnant rats and rabbits received gadofosveset trisodium at various doses up to approximately 11 (rats) and 21.5 (rabbits) times the human dose (based on body surface area). The highest dose resulted in maternal toxicity in both species. In rabbits that received gadofosveset trisodium at 3 times the human dose (based on body surface area), increased post-implantation loss, resorptions, and dead fetuses were observed. Fetal anomalies were not observed in the rat or rabbit offspring. Because pregnant animals received repeated daily doses of ABLAVAR, their overall exposure was significantly higher than that achieved with a single dose administered to humans.

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 risks associated with exposure of infants 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-contrast 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 subjects 65 years and older and younger subjects. Whereas current clinical experience has not identified differences in responses between elderly and younger patients, greater susceptibility to adverse experiences of some older individuals cannot be ruled out.

10 OVERDOSAGE

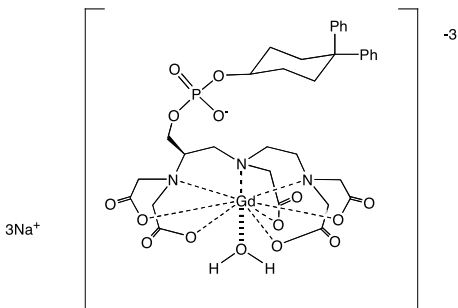
ABLAVAR Injection has been administered to humans up to a dose of 0.15 mmol/kg (5 times the clinical dose). No ABLAVAR overdoses were reported in clinical trials. In the event of an overdose, direct treatment toward the support of all vital functions and prompt institution of symptomatic therapy. Gadofosveset has been shown to be removed by hemodialysis using a high flux dialysis procedure [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

ABLAVAR (gadofosveset trisodium) Injection is a sterile, nonpyrogenic, formulation of a stable gadolinium diethylenetriaminepentaacetic acid (GdDTPA) chelate derivative with a diphenylcyclohexylphosphate group. Each mL of ABLAVAR Injection contains 244 mg of gadofosveset trisodium (0.25 mmol), 0.268 mg of fosveset, and water for injection.

It contains no preservative and the solution pH ranges between 6.5 and 8.0.

Gadofosveset trisodium is chemically trisodium-[(2-(R)-[(4,4-diphenylcyclohexyl) phosphonoxy]methyl]-diethylenetriaminepentaacetate) (aquo) gadolinium(III), with a molecular weight of 975.88 g/mol, and an empirical formula of $C_{23}H_{40}GdN_3Na_3O_{13}P$. It has a structural formula:



Pertinent physicochemical data of ABLAVAR Injection are provided below:

Table 3. Physicochemical Characteristics

Parameter	Condition	Value
Osmolality (mOsmol/kg water)	@ 37°C	825
Viscosity (cP)	@ 20°C	3.0
Density (g/mL)	@ 25°C	1.1224

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Following intravenous injection, gadofosveset binds reversibly to endogenous serum albumin resulting in longer vascular residence time than non-protein binding contrast agents. The binding to serum albumin also increases the magnetic resonance relaxivity of gadofosveset and decreases the relaxation time (T1) of water protons resulting in an increase in signal intensity (brightness) of blood.

12.2 Pharmacodynamics

In human studies, gadofosveset substantially shortened blood T1 values for up to 4 hours after intravenous bolus injection. Relaxivity in plasma was measured to be 33.4 to 45.7 mM⁻¹s⁻¹ (0.47 T) over the dose range of up to 0.05 mmol/kg.

12.3 Pharmacokinetics

The pharmacokinetics of intravenously administered gadofosveset conforms to a two-compartment open model with mean plasma concentrations (reported as mean ±SD) of 0.43 ± 0.04 mmol/L at 3 minutes post-injection, and 0.24 ± 0.03 mmol/L at one hour post-injection. The mean half-life of the distribution phase is 0.48 ± 0.11 hours and the mean half-life of the elimination phase is 16.3 ± 2.6 hours. The mean total clearance of gadofosveset is 6.57 ± 0.97 mL/h/kg following the administration of 0.03 mmol/kg.

Distribution: The mean volume of distribution at steady state for gadofosveset was 148 ± 16 mL/kg, roughly equivalent to that of extracellular fluid. A significant portion of circulating gadofosveset is bound to plasma proteins, predominantly 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 79% and 94% (mean of 83.7%) of an injected dose recovered in the urine. Of the total quantity of circulating gadofosveset recovered in urine, 94% is recovered within the first 72 hours. A small portion of gadofosveset dose is recovered in feces (approximately 4.7%).

Special Populations

Renal Insufficiency: Administration of gadolinium-based contrast agents, including ABLAVAR to patients with severe renal insufficiency increases the risk for NSF. Administration of these agents to patients with mild to moderate renal insufficiency may increase the risk for worsened renal function [see *Warnings and Precautions* (5.1 and 5.3)]. Prior to use of ABLAVAR in these patients, ensure that no satisfactory diagnostic alternatives are available. In patients with moderate to severe renal impairment (glomerular filtration rate < 60 mL/kg/m²), administer ABLAVAR at a dose of 0.01 mmol/kg to 0.02 mmol/kg. Consider follow-up renal function assessments following ABLAVAR administration to any patients with renal insufficiency.

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 (AUC) increased almost 1.75-fold in patients with moderate (creatinine clearance: 30 to 50 mL/min) and 2.25-fold in patients with severe renal impairment (creatinine clearance < 30 mL/min). The elimination half-life increased from 19 hours in normal subjects to 49 hours in patients with moderate and 70 hours in patients with severe renal impairment. The volume of distribution at steady state and plasma protein binding of gadofosveset were not affected by renal impairment. Fecal elimination of gadofosveset increased as a function of increasing renal impairment (6.5% in normal subjects to 13.3% in patients with severe renal impairment).

Hemodialysis: Gadofosveset is removed from the body by hemodialysis using high-flux filters. Elimination of the total administered dose of gadolinium in dialysate over 3 dialysis sessions using high-flux filters averaged 46.8%, 12.9%, and 6.11% 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.

Geriatric: No dosage adjustment is necessary based on age. Age 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 bacterial reverse mutation assay, CHO chromosome aberration assay, and the in vivo mouse micronucleus assay. Administration of up to 1.5 mmol/kg (8.3 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 comparisons of sensitivity and specificity between MRA with and without ABLAVAR, with 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 the aortoiliac region. The interpretation 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 424 patients, the median 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 68% were 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.

Superiority in sensitivity and non-inferiority in 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.

Table 4. Performance Characteristics of ABLAVAR-MRA and Non-contrast MRA

Reader	SENSITIVITY			SPECIFICITY		
	ABLAVAR-MRA [A]	Non-contrast MRA [B]	[A] - [B] (95% CI)*	ABLAVAR-MRA [A]	Non-contrast MRA [B]	[A] - [B] (95% CI)*
1	89%	69%	20% (15%,25%)	72%	71%	1% (-3%,5%)
2	82%	70%	12% (7%,17%)	81%	73%	8% (4%,12%)
3	79%	64%	15% (9%,21%)	85%	85%	0% (-2%,2%)

* (Based on cluster-corrected McNemar Test)

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 72% [95% CI (54%, 90%)] to 97% [95% CI (93%, 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, clear, 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 vials packages of 10 vials
NDC 11994-012-02 - 15 mL fills in 20 mL single use vials in packages of 10 vials

Store ABLAVAR Injection up to 25°C (77°F; excursions permitted to 15 to 30°C [59 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 allergic respiratory disorder
- have a history of kidney and/or liver disease
- have recently received a gadolinium-based contrast agent
- have a history of heart rhythm disturbances, or cardiac disease
- are taking any prescription or over-the-counter medications

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

- Describe the clinical 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:

- reactions at the injection site, such as: redness, mild and transient burning or pain or feeling of warmth or coldness
- side effects of itching or nausea



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