DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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/1.73m^2) 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

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 increase the risk of nephrogenic systemic fibrosis (NSF) in patients with:

- **acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m^2), or**
- **acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.**

In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any re-administration [*see Warnings and Precautions (5.1)*]

----------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 aortoiliac occlusive disease (AIOD) 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 may result from administration of gadolinium-based contrast agents to certain patients (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: [10/2009]

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FULL PRESCRIBING INFORMATION

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:

- **acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m^2), or**
- **acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.**

In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any 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 aortoiliac occlusive disease (AIOD) 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)**	**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

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

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m^2) and in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced MRA. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a gadolinium-based contrast agent in order to enhance the contrast agent's elimination. Ablavar binds to blood albumin and use of a high-flux dialysis procedure is essential to optimize Ablavar elimination in patients receiving chronic hemodialysis. The usefulness of hemodialysis in the prevention of NSF is unknown [*see Boxed Warning and Clinical Pharmacology (12.3)*].

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a gadolinium-based contrast agent and the degree of renal function impairment at the time of exposure.

Post-marketing reports have identified the development of NSF following single and multiple administrations of gadolinium-based contrast agents. These reports have not always identified a specific agent. Prior to marketing of Ablavar, where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan™), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following sequential administrations of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®). The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific gadolinium-based contrast agent.

The extent of risk for NSF following exposure to any specific gadolinium-based contrast agent is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006; 17:2359). The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent prior to any re-administration. NSF was not reported in clinical trials of Ablavar [*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.

8.3 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

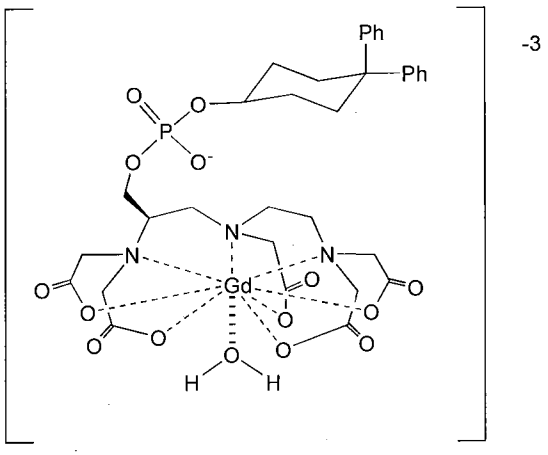
Ablavar Injection has been administered to humans up to a dose of 0.15 mmol/kg (5 times the clinical dose). No Ablavar overdoses were reported in clinical trials. In the event of an overdose, direct treatment toward the support of all vital functions and prompt institution of symptomatic therapy. Gadofosveset 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) phosphonooxymethyl]-diethylenetriaminepentaacetato)(aquo) gadolinium(III),with a molecular weight of 975.88 g/mol, and an empirical formula of $C_{33}H_{40}GdN_3Na_3O_{15}P$. It has a structural formula:



Pertinent physiochemical data of Ablavar Injection are provided below:

Table 3. Physiochemical 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 $mM^{-1}s^{-1}$ (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 approximately 83.5% of an injected dose excreted in the urine over 14 days. Ninety-four percent (94%) of urinary excretion occurs in 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, *in vitro* 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

Gadolinium-based contrast agents, including Ablavar, increase the risk for NSF in patients with severe renal insufficiency or acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative setting of liver transplantation. Patients with less severe renal insufficiency who receive repetitive administrations of a gadolinium-based contrast agent may have an increased risk for the development of NSF, especially if the time interval between the administrations precludes clearance of the previously administered contrast agent from the body. If Ablavar is administered in these situations, instruct patients to contact their physician or healthcare provider if they develop signs or symptoms of NSF, 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 of the arms, hands, legs, or feet, pain deep in the hip bones or ribs, or muscle weakness [*see Warnings and Precautions (5.1)*].

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

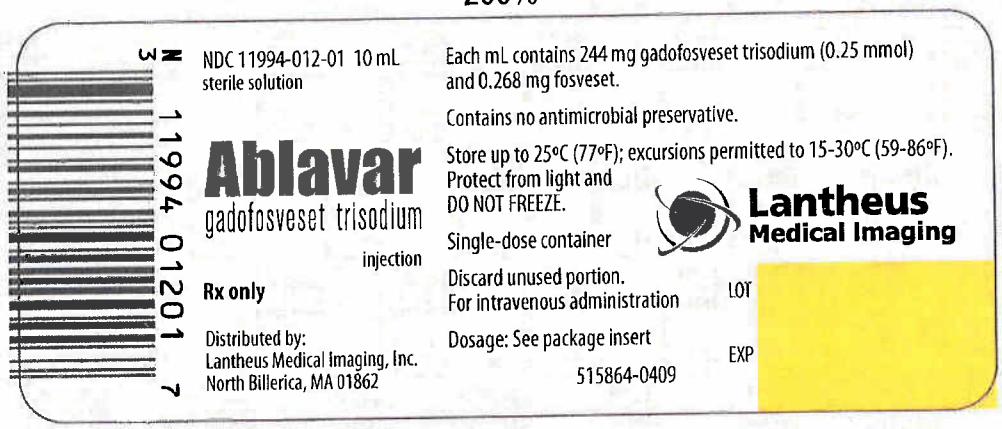
Distributed by Lantheus Medical Imaging, Inc., 331 Treble Cove Road, North Billerica, MA 01862, United States

US Patents: 7,060,250; 7,229,606; and 5,919,967

515862-1009 November, 2009

Ablavar DRAFT
10 mL Label

200%



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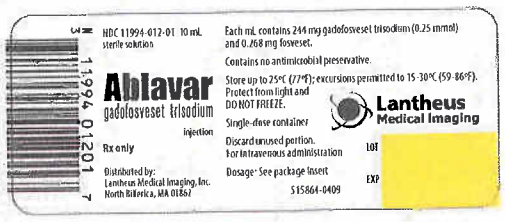

Ablavar DRAFT
10mL Shipper Label

100%

NDC 11994-012-01
sterile solution

Ablavar
gadofosveset trisodium
Rx only

10 x 10 mL
244/0.268 mg/mL

Each mL contains 244 mg gadofosveset trisodium (0.25 mmol) and 0.268 mg fosveset.

Contains no antimicrobial preservative.

Store up to 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light and DO NOT FREEZE.

Single-dose container

Discard unused portion.
For intravenous administration

Dosage: See package insert

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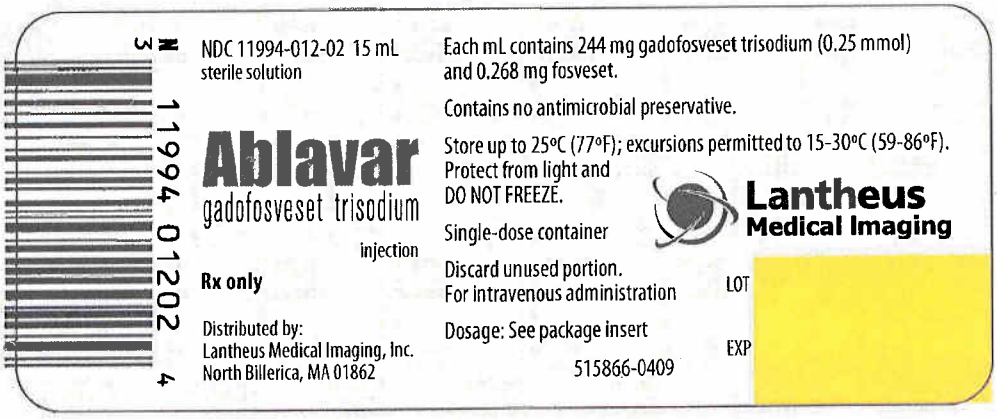
Ablavar DRAFT
15 mL Label

200%



100%

Ablavar DRAFT
15mL Shipper Label

100%

NDC 11994-012-02
sterile solution

Ablavar
gadofosveset trisodium
Rx only

10 x 15 mL
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Discard unused portion.
For intravenous administration

Dosage: See package insert

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

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/s/

JAMES W MOORE
01/11/2010

RAFEL D RIEVES
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