

Material Safety Data Sheet

1. PRODUCT AND COMPANY IDENTIFICATION	
<i>Product Information</i>	
Product Name	Ablavar®
Version	1.0, 6/24/09
Synonyms	MS-325 Injection, Gadofosveset Trisodium Injectable Solution
Product Uses	This material is used as a medical imaging agent.
<i>Company Identification</i>	
Address	Lantheus Medical Imaging 331 Treble Cove Road Billerica, MA 01862 United States Of America 1-800-299-3431
Emergency Phone Number	CHEMTREC 1-800-424-9300. For all international transportation emergency call CHEMTREC at 1-703-527-3887. Collect calls accepted.

2. COMPOSITION INFORMATION ON INGREDIENTS		
Components	Concentration	CAS No.
<i>Hazardous Components</i>		
Gadofosveset trisodium:	20 – 21%	211570-55-7
Fosveset	< 0.1 %	193901-91-6
<i>Other Ingredients</i>		
Water	> 79 - 80%	7732-18-5

3. HAZARDS IDENTIFICATION	
<i>Emergency Overview</i>	
Appearance	Liquid: clear, colorless to slightly yellow
Signal Word	Caution!
Hazard Statements	May be harmful if inhaled, ingested or in contact with the skin. May cause allergic sensitization. Exposure poses increased risk for persons with severe kidney dysfunction. See Section 10.
Precautionary Measures	Avoid ingestion, inhalation, skin and eye contact. Wash hands after handling to minimize exposure.
<i>Potential Health Effects</i>	
Eyes	Not available.
Skin	Not available.
Ingestion	Not available.
Inhalation	Not available.
Target Organs	Kidneys, lungs, lymph nodes.
Signs and Symptoms	Acute: may cause itching, tingling or prickling sensation, salivation, nausea, vomiting, pupil dilation, convulsions, nose bleeds, tremors, prostration.
<i>Environmental Effects</i>	Not available

4. FIRST AID MEASURES	
Eye contact	Rinse immediately with plenty of water for at least 15 minutes. Keep eye wide open while rinsing. Obtain medical attention.

Skin contact	Wash off immediately with plenty of water for at least 15 minutes. If skin irritation occurs, get medical advice/attention.
Inhalation	Move to fresh air. Oxygen or artificial respiration if needed. Obtain medical attention.
Ingestion	Obtain medical attention. Do NOT induce vomiting. Never give anything by mouth to an unconscious person.
Notes to Physicians	This material is used as a medical imaging agent. This product, by intravenous doses in animals far above those used for medical imaging, itching, tingling or prickling sensation, salivation, nausea, vomiting, pupil dilation, convulsions, nose bleeds, tremors, prostration, death. Material not fully tested. Refer to Section 10.
Medical Surveillance	Employees, who are pregnant, are breast-feeding, or who are concerned with other reproductive issues should be encouraged to consult with the occupational health physician monitoring worker's health.

5. FIRE-FIGHTING MEASURES

Flammable Properties	Not available.
Extinguishing Media	Suitable extinguishing media: Dry chemical, Water spray, Foam Unsuitable extinguishing media: Do NOT use water jet.
Protection of Firefighters	Specific hazards: Not available Protective equipment: Use personal protective equipment. In the event of fire, wear self-contained breathing apparatus. Hazardous Combustion Products: Not available
Other Information	Decontaminate protective clothing and equipment before reuse.

6. ACCIDENTAL RELEASE MEASURES

Personal Precautions	Refer to protective measures listed in sections 7 and 8. Use personal protective equipment. Examples include tightly fitting safety goggles, lab coat and impervious gloves. Depending on the nature of the spill (quantity and extent of spill) additional protective clothing and equipment such as a self-contained breathing apparatus may be needed.
Environmental Precautions	Prevent release to drains and waterways. Prevent release to the environment.
Containment Methods	Contain spillage, and then collect with non-combustible absorbent material, (e.g. sand, earth, diatomaceous earth, vermiculite) and place in container for disposal according to local/national regulations (see section 12).
Cleanup Methods	Contain and collect spillage and place in container for disposal according to local regulations (see Section 12). Handle waste materials, including gloves, protective clothing, contaminated spill cleanup material, etc., as appropriate for chemically and pharmacologically similar materials.

7. HANDLING AND STORAGE

Handling Precautions	Avoid exposure - obtain special instructions before use. Avoid inhalation. Keep away from heat and sources of ignition. Prevent release to drains and waterways.
Storage Conditions	Keep in a tightly closed container, stored in a cool, dry, ventilated area. Protect against physical damage. Containers of this material may be hazardous when empty since they retain product residues (dust, solids); observe all warnings and precautions listed for the product.
Container Requirements	Store in original container. Keep away from heat, sparks and flames.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION				
Exposure Limit(s)	Company Guideline	ACGIH	OSHA	NIOSH
Gadofosveset trisodium:	0.15 mg/m ³	---	---	---
Fosveset:	---	---	---	---
Lantheus Medical Imaging Exposure Guidelines Summary	Control exposures to Gadofosveset trisodium below 0.15 mg/m ³ 8 hr TWA			
Recommended Industrial Hygiene Monitoring Methods	Non-available.			
Engineering Controls and Ventilation	When handling small quantities in a clinical setting, good room ventilation is desirable. Specific engineering controls should not be needed. When handling larger quantities, such as in a manufacturing setting, ensure worker exposure is below the recommended exposure limit. If significant aerosol (dust) is generated, use local exhaust ventilation, process enclosures, containment technology, or other engineering controls to keep airborne levels below recommended exposure limit.			
Respiratory Protection	Respiratory protection is not required for normal use of this material. If the occupational exposure control limit (ECL) is exceeded, wear an appropriate respirator with a protection factor sufficient to control exposures to below the ECL.			
Eye Protection	Follow good chemical hygiene practices when using clinical or consumer presentations. Glasses or goggles are recommended if eye contact is possible.			
Hand Protection	Follow good chemical hygiene practices when using clinical or consumer presentations. Wear gloves when working with large quantities.			
Skin and Body Protection	Follow good chemical hygiene practices when using clinical or consumer presentations. It is recommended that a laboratory coat be worn when handling product.			
Hygiene	Wash hands and face before breaks and immediately after handling the product.			

9. PHYSICAL AND CHEMICAL PROPERTIES	
<i>Appearance</i>	
Physical State	Liquid
Color	Clear, colorless to slightly yellow
<i>Descriptive Properties</i>	
Molecular Weight	975.88, 957.86 (anhydrous form)
Odor	Odorless
pH	6.5 – 8.0

9. STABILITY AND REACTIVITY	
Chemical Stability	Stable under normal conditions.
Conditions to Avoid	Not available
Incompatible Products	Not available
Hazardous Decomposition Products	Hazardous decomposition products formed under fire conditions: Not available
Hazardous Reactions	None known. Stable under normal conditions. Hazardous polymerization does not occur.

10. TOXICOLOGICAL INFORMATION	
Routes of Entry	Ingestion, Inhalation, Eye Contact, Skin Contact
Eye Irritation	Not available
Skin Irritation	Not available
Respiratory Irritation	Not available
Sensitization	May cause sensitization in susceptible individuals.
Acute Toxicity Study	Acute toxicity (other routes of administration) Gadofosveset trisodium: LD ₅₀ (rat, intravenous): 2.9 g/kg
Repeated Dose Toxicity	Gadofosveset trisodium: 1 months intravenous (daily) rat study : NOEL = 9.76 mg/kg, NOAEL = 97.6 mg/kg Effects included vacuolation of the kidney cortical tubular epithelial cells of the proximal convoluted tubules, pale kidneys, and increased kidney weights, accumulation of vacuolated macrophages in the lungs, vacuolated reticuloendothelial cells in several tissues and vacuolated odontoblasts in the incisors. Histopathological changes persisted in the kidneys, lymph nodes, and adrenal medulla. 1 months intravenous (daily) monkey study: NOAEL: 97.6 mg/kg. Effects included: increased sialorrhea and vomiting (the latter only observed once in one male); tubular vacuolation of the proximal part (slight to moderate in male animals, minimal in female animals) In the high dose of 2.0 mmol/kg: frequent vomiting in both sexes and with high incidence followed by a decrease in food consumption and decrease in body weight gain and body weight loss; increase in monocyte count in males and females on day 24; increase in aspartate aminotransferase (AST) in males and females on days 2 and 24; increases in alpha- and beta-globulins in males and females on day 24; decrease in albumin in males and females on day 24; vacuolation of proximal renal tubules (massive), bladder urothel, lymph nodes (accompanied by histiocytosis), pancreatic islet, periportal hepatocytes and lung alveolar macrophages; further histological changes in the liver. The reported clinical observations and the changes in hematology and clinical chemistry were no longer visible after the 12 weeks recovery period. Findings which persisted after the 12 week recovery period were a minimal tubular vacuolation of the kidneys (proximal part) and minimal histiocytosis accompanied by vacuolation in some lymph nodes.
Genetic Toxicity	Gadofosveset trisodium: The mutagenicity potential of Gadofosveset trisodium was evaluated using two <i>in vitro</i> assays (the reverse mutation assay and chromosomal aberrations in CHO cells) and one <i>in vivo</i> assay (mouse bone marrow micronucleus assay). In all studies, Gadofosveset trisodium was not mutagenic under the conditions of these studies.

Carcinogenicity		Not available		
	ACGIH	OSHA	NTP	IARC
Gadofosveset trisodium	---	---	---	---
Fosveset	---	---	---	---
Reproductive/Developmental Toxicity	<p>Gadofosveset trisodium:</p> <p>At 1.5 mmol/kg/day (4 weeks in males, 2 weeks in females) in Sprague-Dawley rats, the number of spermatids per gram of testicular tissue was reduced and reduced epididymides weight. Fertility was not reduced at this dose. This same dose caused some deaths, pale kidneys and in one case, enlarged kidneys in the test animals. The NOAEL for this study was 0.21 mmol/kg.</p> <p>In rat embryotoxicity studies, Gadofosveset trisodium at 2.0 mmol/kg/day for 11 days caused embryotoxicity in the form of an increased rate of skeletal variations and retardations. This dose also produced signs of maternal toxicity in the form of a slight reduction in food intake, a marginal body weight reduction, reduced body weight gain, reduced carcass weight, pale and heavier kidneys. The NOAEL for this study was 0.45 mmol/kg.</p> <p>In rabbits, an increased mean incidence of post-implantation loss caused by an increased number of early resorptions was observed in dams treated with Gadofosveset trisodium at 2 mmol/kg/day. Maternal toxicity was also noted at this dose in the form of increase kidney weight. The post-implantation loss was associated with a decrease in the number of fetuses and a decrease in the gravid uterus weight.</p>			
Conditions that may be aggravated by exposure to this material:	<p>The US FDA has requested that a boxed warning be added to the labeling of all gadolinium-based MRI contrast agents marketed in the US; the boxed warning describes the risk for nephrogenic systemic fibrosis (NSF) in patients receiving these agents with renal dysfunction that meets one of the following two conditions:</p> <ul style="list-style-type: none"> • acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m²); • acute renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period of any severity. <p>In patients with renal insufficiency, acute renal failure has occurred with the use of other gadolinium agents. The risk of renal failure may increase with increasing dose of gadolinium</p>			

	contrast. <i>Persons with these conditions should not be exposed to this material at any level except as recommended by a physician.</i>
	Clinical Trials Gadofosveset trisodium: At the proposed clinical dose (0.03 mmol/kg), 36.0% patients experienced at least one AE, and 23.6% experienced at least one treatment-related AE. The adverse effects profile of Gadofosveset trisodium Injection is one of generally mild, rapid onset, short duration events. The treatment related events were pruritus NOS, paresthesia, nausea, vasodilatation, and burning sensation NOS. With the exception of pruritus, these events are similar to those commonly associated with gadolinium-based contrast media. In clinical trials, a QTc change of 30 to 60 msec from baseline was observed in 6% of patients at 45 minutes post injection. This prolongation was not associated with arrhythmias or other symptoms. In clinical trials, anaphylactoid and/or anaphylactic reactions occurred in two of 1676 subjects.
Target Organs	Gadofosveset trisodium: Kidneys, lungs, lymph nodes
Symptoms	Gadofosveset trisodium: See "Clinical Trials".
Other Toxicity Information	<u>Not available</u>

11. ECOLOGICAL INFORMATION	
Ecotoxicological Information (Aquatic)	Not available
Ecotoxicological Information (Terrestrial)	Not available
Chemical Fate	Not available.

12. DISPOSAL CONSIDERATIONS	
Advice on Disposal and Packaging	Disposal should be in accordance with applicable regional, national, and local laws and regulations. Local regulations may be more stringent than regional or national requirements.

13. TRANSPORT INFORMATION	
<i>Transportation Classification for All Modes:</i> This material is not a dangerous good for the purpose of transportation.	

14. REGULATORY INFORMATION	
United States of America	
OSHA Hazard Classification	Hazardous, Target Organs
313 Toxic Release Inventory. Listed Chemicals/Compounds	No components listed on the SARA 313 inventory.
TSCA Inventory	No
International	
Canada	

WHMIS	This MSDS has been prepared according to the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all of the information required by the CPR.
DSL/NDSL	No
Mexico	
Mexico Classification	Health classification - Minimal hazard - 0 - Substances that do not pose a hazard under emergency conditions other than that of ordinary combustible materials.

15. OTHER INFORMATION	
MSDS preparation information	
Prepared by	Environment, Health and Safety 1-978-671-8673
Prepared on	6/24/09
The information contained in this MSDS is believed to be accurate and represents the best information reasonably available at the time of preparation. However, we make no warranty, express or implied, with respect to such information. and we assume no liability from its use.	

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

- acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m²), 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 aortic 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]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

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/1.73m²), 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)].

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Ablavar is indicated for use as a contrast agent in magnetic resonance angiography (MRA) to evaluate aortic 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/1.73m²) 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 of 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

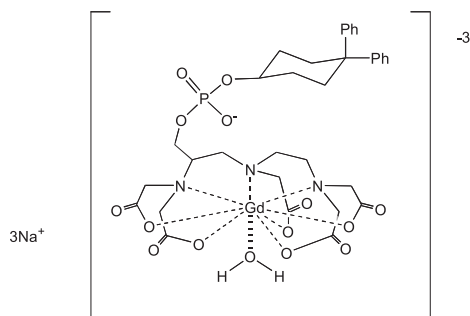
Ablavar Injection has been administered to humans up to a dose of 0.15 mmol/kg (5 times the clinical dose). No Ablavar overdoses were reported in clinical trials. In the event of an overdose, direct treatment toward the support of all vital functions and prompt institution of symptomatic therapy. Gadofosveset 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) phosphonoxy]methyl]-diethylenetriaminepentaacetate) (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 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 $\text{mM}^{-1}\text{s}^{-1}$ (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 \pm 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, 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 ($\geq 50\%$ 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



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