DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Ms. June Bray
Director, Regulatory Affairs
Berlex Laboratories, Inc.
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

RE: **NDA 19-596**
Magnevist (gadopentetate dimeglumine) Injection
MACMIS # 10157

Dear Ms. Bray:

This letter objects to Berlex Laboratories, Inc.'s (Berlex) dissemination of violative promotional materials for Magnevist. Specifically, as part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC), has identified a brochure (00-MAG-053) submitted under cover of Form FDA 2253 that is false or misleading under the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Our specific objections follow:

Promotion of Unapproved New Uses—Breast and Musculoskeletal Imaging

Promotional materials are false or misleading if they contain suggestions or representations not approved or permitted in the approved package insert (PI), that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence. Your brochure is violative because it states that Magnevist is useful for breast imaging and musculoskeletal imaging when such has not been demonstrated by substantial evidence.

For example, in a table on page 2, you present a heading "Broad Indications" and compare the indications of Magnevist to Prohance (gadoteridol injection), Omniscan (gadodiamide injection), and Optimark (gadoversetamide injection). In the table, you show that Magnevist and Omniscan are indicated for abdominal, pelvis, thorax, retroperitoneal, and pediatric imaging. You also show that **only** Magnevist is indicated for musculoskeletal, and breast imaging (emphasis added). However, Magnevist is not approved for use to image the breast or musculoskeletal areas of the body. Also on page 4, you state that Magnevist is indicated "for adult whole body imaging." Your addition of the term "whole" to your approved indication for imaging the "body" also implies that the drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence. Thus, your brochure is misleading because it promotes unapproved new uses for Magnevist.

We are especially concerned with Berlex's promotion of these unapproved new uses for Magnevist considering the fact that the Agency and Berlex have discussed Magnevist's approved indications. We have previously advised you that your database for imaging breast (8 patients) and musculoskeletal tissue (22 patients), described in the clinical trials section of your labeling, is inadequate to support the safety and efficacy of Magnevist for these uses.

We are also concerned because your violative promotion of Magnevist for unapproved new uses continues despite our previous written objections. Specifically, in our letter to you dated April 15, 1999, we objected to your promotional brochure that presented two case studies regarding imaging the carotid arteries, an unapproved new use. You claimed in that brochure that Magnevist in magnetic resonance arteriography could: 1) identify stenosis and its severity in the carotid arteries, 2) assess other arteries including the proximal common carotid artery, and 3) confirm ultrasound, which may obviate the need for angiography. These claims also are not supported by substantial evidence.

In that same letter, we objected to your dissemination of a poster including an unlabeled MRI image of angiography, presumably of the aorta and iliac arteries.

We stated that you have no basis to promote Magnevist for magnetic resonance arteriography (MRA), and specifically we were not aware of evidence to support the efficacy of Magnevist for MRA. You assured us that you would cease using the violative materials.

Unapproved Dosing Regimen

Your brochure is misleading because it suggests that Magnevist has a flexible dosing regimen and is approved for single dose injections of 0.3 mmol/kg. As you know, Magnevist only has a recommended dosing and administration regimen of 0.1 mmol/kg body weight administered at a rate not to exceed 10 mL per 15 seconds.[1] However, you claim in a table on page 3 of the brochure that Magnevist has "High Dose Safety" at 0.3 mmol/kg single dose injection, i.e., 3 times the recommended dose. This misleading claim takes a statement out of context from the clinical trials section of the PI and implies that Magnevist is efficacious for single dose injections of 0.3 mmol/kg.

We are particularly concerned about this promotional claim because there may be a hazard using Magnevist at dosages and rates inconsistent with its approved labeling. Magnevist has not been shown to be safe at higher rates of injection. It is known that Magnevist is associated with vascular related adverse events. In fact, your PI has warnings regarding patients with predisposition to the development of thrombotic syndromes, and includes a precaution that cases of phlebitis and thrombophlebitis have been reported in association with Magnevist that have resulted in amputation of the dosed limb.

[1] The maximum approved volume is 26 mL.

Misleading Safety Presentation

Promotional materials are false or misleading if they contain suggestions or representations not approved or permitted in the approved product labeling (PI), that a drug is safer, has fewer, or less incidence of, or less serious side effects than has been demonstrated by substantial evidence. On page 2 you claim that Magnevist has proven safety based on a well-documented global profile. You further claim its injection safety record provided a positive clinical experience in more than 20 million patients. You present the drug's most frequently reported adverse experiences from clinical trials, but fail to provide important information from the PI regarding its injection safety record. Specifically, there have been cases associated with the use of Magnevist where patients have had severe cases of phlebitis and thrombophlebitis resulting in surgical intervention, including compartment release or amputation of the dosed limb.

Lack of Fair Balance

Promotional materials are misleading if they fail to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. On page 5 of the brochure, you present the abbreviated indications for Magnevist (gadopentetate dimeglumine) Injection, as well as for your drug products Ultravist (iopromide) Injection, Feridex I.V. (ferumoxides injectable solution), Quadramet (Samarium Sm-153 Lexidronam Injection), Neotect (Kit for the preparation of Technetium Tc-99m Depreotide Injection), and Acutect (Kit for the preparation of Technetium Tc-99m Apcitide Injection). Although you present risk information at the bottom of the page regarding each of these drug products, the information is presented in a manner that is not reasonably comparable to your presentation relating to the effectiveness of the drug thereby minimizing its importance.

Further, we note that you misrepresented the indication for Neotect by claiming that it is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence. The drug is indicated for identifying somatostatin receptor-bearing pulmonary masses in patients presenting with pulmonary lesions on CT or x-ray who have shown malignancy or who are highly suspect for malignancy. However, you claim that the drug is used in patients with pulmonary lesions on CT and/or X-ray who have either known or suspected malignancy. The drug is approved for use in a much different population.

Requested Actions

In order to address these objections, we request that you immediately cease the dissemination of this violative brochure and all similar promotional materials that contain the same or similar messages.

You should respond in writing to us regarding this issue by December 5, 2001. Your response should include Berlex's intent to comply with the above request, the date that it ceased disseminating these and any other violative promotional materials with the same or similar messages, and a list of the discontinued materials.

If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Berlex that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 10157 and NDA 19-596.

Sincerely,

{See appended electronic signature page}

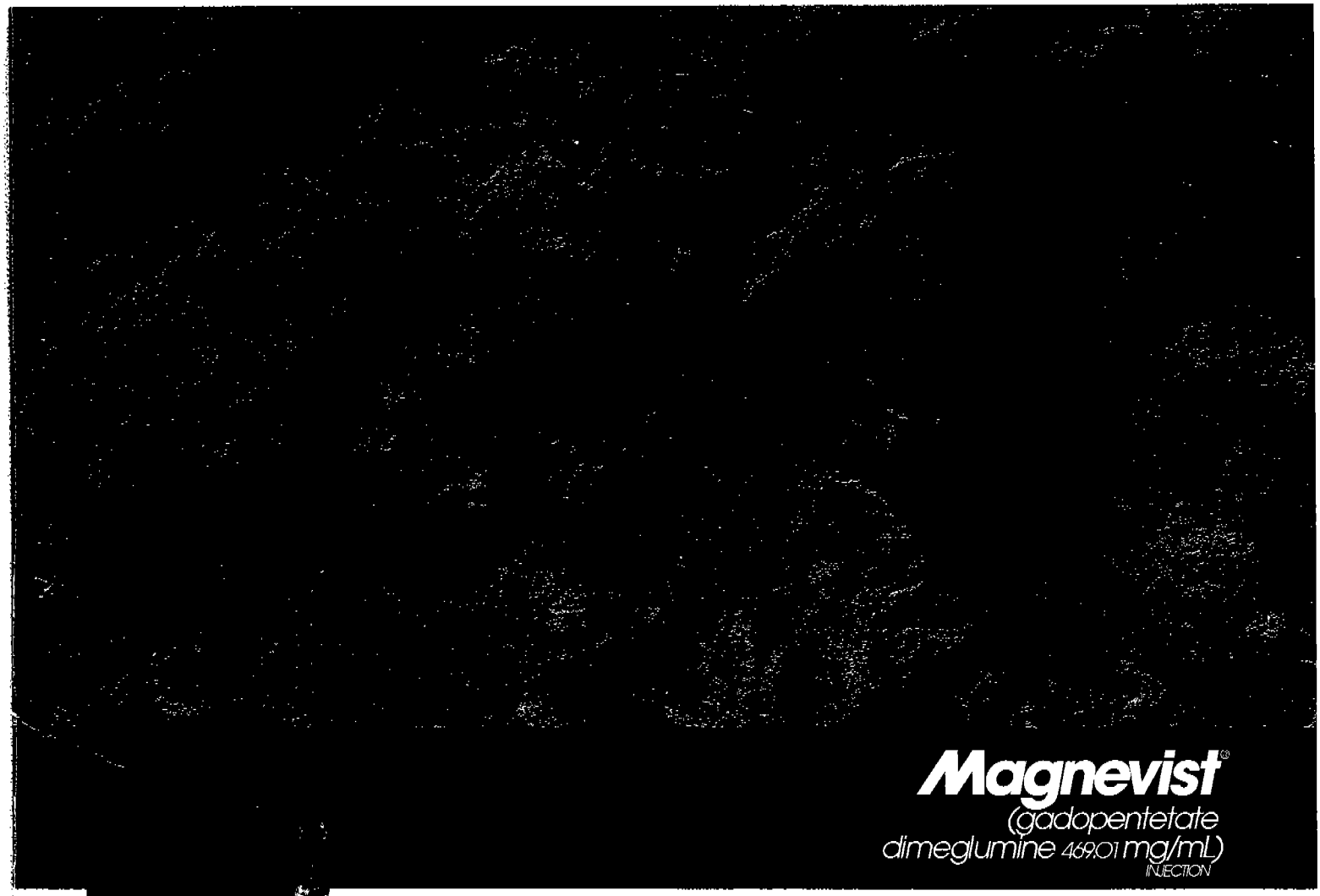
Warren Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Warren Rumble
11/20/01 01:01:04 PM

ENHANCE WITH CONFIDENCE



BERLEX® IMAGING

Everything you need to see

PROVEN SAFETY

Patient safety and tolerance are proven based on a well-documented global clinical profile. MAGNEVIST® (gadopentetate dimeglumine) injection was well-tolerated in clinical trials encompassing nearly 1,000 patients.[1]

Most Frequently Reported Adverse Experiences For All Trials Adult/Pediatric CNS Plus Body

Headache 4.8%

Nausea 2.7%

Injection-site coldness/localized coldness 2.3%

The MAGNEVIST® (gadopentetate dimeglumine) Injection Safety Record

- Positive clinical experience in more than 20 million patients worldwide, including over 16 million in the US[1]
- Twelve years of consistent product quality

[1] Data on file, Berlex Laboratories, Inc.

BROAD INDICATIONS

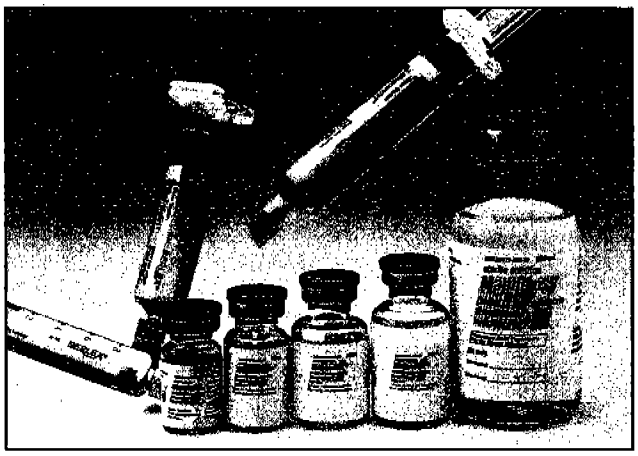
		PROHANCE®* (gadoteridol)	OMNISCAN®† (gadodiamide) injection	OPTIMARK®‡ (gadoversetamide injection)
CNS				
Brain		X	X	X
Spine		X	X	X
Pediatric		X	X	
HEAD AND NECK		X		
BODY§				X (Liver Only)
Abdominal			X	
Pelvis			X	
Thorax			X	
Retroperitoneal			X	
Musculoskeletal				
Breast				
Pediatric			X	

* PROHANCE® is a trademark of Bracco Diagnostics, Inc.
† OMNISCAN® is a trademark of Nycomed, Inc.
‡ OPTIMARK® is a trademark of Mallinckrodt Medical, Inc.
§ Body area studied during clinical trials.

Please see accompanying full prescribing information.

FLEXIBLE DOSING

Product	Indication	Efficacy Data	High Dose Safety
MAGNEVIST® (gadopentetate dimeglumine) injection	0.1 mmol/kg CNS and Body		0.3 mmol/kg Single Dose Injection
PROHANCE®* (gadoteridol)	0.1 mmol/kg CNS	0.1 mmol/kg a second dose of 0.2 mmol/kg may be given up to 30 min CNS (cerebral METS only)	—
OMNISCAN®† (gadodiamide) injection	0.1 mmol/kg CNS and Body	0.1 mmol/kg a second dose of 0.2 mmol/kg may be given within 20 min CNS (cerebral METS only)	—
OPTIMARK®‡ (gadoversetamide injection)	0.1 mmol/kg CNS and Liver	—	—



MAGNEVIST® (gadopentetate dimeglumine) injection is the only paramagnetic agent which has an established safety of 0.3 mmol/kg dose administered as a single injection as proven in clinical trials.

* PROHANCE® is a trademark of Bracco Diagnostics, Inc.
† OMNISCAN® is a trademark of Nycomed, Inc.
‡ OPTIMARK® is a trademark of Mallinckrodt Medical, Inc.

PACKAGING OPTIONS FOR CONVENIENCE

MAGNEVIST®
(gadopentetate dimeglumine) Injection
Presentations

Vials	Prefilled Syringes	Pharmacy Bulk Package
5 mL vials 10 mL vials 15 mL vials 20 mL vials	10 mL syringes 15 mL syringes 20 mL syringes	100 mL vials (the only paramagnetic contrast agent to offer this size)

- Convenient and effective administration
- Wide range of sizes and packaging options to meet dosing needs
- Convenient pediatric use

MAGNEVIST® (gadopentetate dimeglumine) injection is the only paramagnetic contrast agent to offer a 100 mL pharmacy bulk package.

MAGNEVIST® (GADOPENTETATE DIMEGLUMINE) INJECTION ...THE LEADER IN THE FIELD[2]

Since being introduced as the world's first MRI enhancement agent, MAGNEVIST® (gadopentetate dimeglumine) injection* has set the standard. It consistently provides unsurpassed definition of difficult-to-see lesions, and has been used routinely in more than 20 million patients worldwide. The MAGNEVIST® (gadopentetate dimeglumine) injection experience is one of expanding diagnostic utility:

1988 - Indications for the adult CNS

1989 - Indications for pediatric brain and spine

1993 - Indications for adult whole body imaging

1995 - Berlex partners with sister company, Medrad®, to expand access to MRI injection systems

1996 - Berlex forms alliance with Abbott Laboratories to optimize service and distribution
- Indications for head and neck

1998 - First decade of use completed
- MAGNEVIST® (gadopentetate dimeglumine) injection available in 5 mL vials

1999 - MAGNEVIST® (gadopentetate dimeglumine) injection available in prefilled syringes

2000 - MAGNEVIST® (gadopentetate dimeglumine) injection available in the 100 mL pharmacy bulk package (first and only multi-dose vial)

*As with all paramagnetic agents, caution should be exercised in patients with deoxygenated sickle erythrocytes and renal insufficiency with or without hepatic impairment. As with all contrast media, the possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered.

[2] Arlington Medical Resources, *The Imaging Market Guide*, MAGNEVIST® (gadopentetate dimeglumine) injection had the highest market share based on MR procedural data from January–June, 2000.

Please see accompanying full prescribing information.

Magnevist®
(gadopentetate dimeglumine 469.01 mg/ml)

DEPENDABLE QUALITY AND SERVICE

Berlex has a long tradition of innovation, quality, and service in diagnostic imaging. You can count on:

- Innovative imaging products
  MAGNEVIST® (gadopentetate dimeglumine) injection, the world's first I.V. contrast agent for use in magnetic resonance imaging
  ULTRAVIST® (iopromide) injection, a nonionic, tri-iodinated contrast agent for use in computed tomography
  FERIDEX I.V.®[3] (ferumoxides injectable solution), the world's first liver-specific MRI enhancement agent
  QUADRAMET® (Samarium Sm-153 Lexidronam Injection), for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan
  NEOTECT™ (Kit for the Preparation of Technetium Tc 99m Depreotide Injection), a scintigraphic imaging agent that works by identifying somatostatin receptor-bearing masses in the lungs, and is used in patients with pulmonary lesions on CT and/or X-ray who have either known or suspected malignancy
  ACUTECT® (Kit for the Preparation of Technetium Tc 99m Apcitide Injection), the first radiopharmaceutical to target acute deep vein thrombosis (DVT)
- Many new products on the horizon including vascular imaging agents
- A dedicated team of professional Sales Consultants ranked best in industry for technical knowledge by MRI radiologists and radiological technologists[4]
- Service and support through our alliance with Abbott Laboratories
- Access to injector technology through our sister company, Medrad®, the world leader in vascular injector systems and MR surface coils

Magnevist®
(gadopentetate dimeglumine 469.01 mg/mL)
INJECTION

[3] Feridex I.V.® (ferumoxides injectable solution) is a registered trademark of and is marketed under a license from Advanced Magnetics, Inc., Cambridge, MA.

[4] Berlex sales consultants ranked #1 in technical knowledge by MRI radiologists and radiological technologists according to Johnson, Zabor & McManus, Inc. (data on file).

MAGNEVIST® (gadopentetate dimeglumine) injection: As with all paramagnetic agents, caution should be exercised in patients with deoxygenated sickle erythrocytes and renal insufficiency with or without hepatic impairment. As with all contrast media, the possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered.

ULTRAVIST® (iopromide) injection: All nonionic, iodinated contrast media currently available inhibit blood coagulation *in vitro* less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events. As with all iodinated contrast agents, serious or fatal reactions have been associated with their use. ULTRAVIST® (iopromide) injection is not indicated for intrathecal use.

FERIDEX I.V.® (ferumoxides injectable solution): Anaphylactic-like reactions and hypotension have been noted in some patients receiving FERIDEX I.V.® (ferumoxides injectable solution), other iron and dextran containing formulations, or radiographic contrast media. In clinical trials, anaphylactic and allergic adverse events occurred in 11/2240 (0.5%) of the patients who received FERIDEX I.V.® (ferumoxides injectable solution). These events included dyspnea, other respiratory symptoms, angioedema, generalized urticaria, and hypotension; and required treatment.

QUADRAMET® (Samarium Sm-153 Lexidronam Injection) causes bone marrow suppression. Before administration, consideration should be given to the patient's current clinical and hematologic status and bone marrow response history to treatment with myelotoxic agents.

ACUTECT® (Kit for the Preparation of Technetium Tc 99m Apcitide Injection): Clinical follow-up studies of patients with negative ACUTECT® (Kit for the Preparation of Technetium Tc 99m Apcitide Injection) scans have not been performed to determine if negative image findings mean the absence of acute venous thrombosis. If a patient has clinical signs and symptoms of acute venous thrombosis, a clinical management decision to withhold treatment with anticoagulants should not be based on a negative ACUTECT® (Kit for the Preparation of Technetium Tc 99m Apcitide Injection) study alone. After administration of ACUTECT® (Kit for the Preparation of Technetium Tc 99m Apcitide Injection), as with the administration of other intravenous drugs, patients with a history of drug reactions, other allergies, or immune system disorders should be observed for several hours.

NEOTECT™ (Kit for the Preparation of Technetium Tc 99m Depreotide Injection): The clinical benefit of NEOTECT™ (Kit for the Preparation of Technetium Tc 99m Depreotide Injection) as a population-based screening tool has not been studied. NEOTECT™ (Kit for the Preparation of Technetium Tc 99m Depreotide Injection) is not an alternative to CT or biopsy. Like other small peptides, NEOTECT™ (Kit for the Preparation of Technetium Tc 99m Depreotide Injection) may induce hypersensitivity reactions or anaphylactic reactions. Adequate treatment provisions, including epinephrine, should be available for immediate use.

QUADRAMET® (Samarium Sm-153 Lexidronam Injection) is a registered trademark of Dow Chemical Company. Under license from CYTOGEN Corporation. Manufactured by Dupont Pharmaceutical Co. Distributed by Berlex Laboratories, Inc.

ACUTECT® (Kit for the Preparation of Technetium Tc 99m Apcitide Injection) is a registered trademark of Diatide, Inc. Co-promoted by Nycomed Amersham.

NEOTECT™ (Kit for the Preparation of Technetium Tc 99m Depreotide Injection) is a trademark of Diatide, Inc. Co-promoted by Nycomed Amersham.

CUSTOMIZED SUPPORT PROGRAMS

Berlex is the leader in providing customized support programs, including:

- Clinical physician/technologist education and business management programs
- Ongoing support for professional associations and major meetings
- Information about reimbursement issues affecting the delivery of quality, cost-efficient healthcare by calling *1-800-4-BERLEX℠ (1-800-423-7539)*

Order through the Berlex/Abbott alliance by calling:
1-888-BERLEX-4, press 1, or 1-800-ABBOTT-3, press 2.

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