

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019596/S08/S09

Trade Name: MAGNEVIST

Generic Name: GADOPENTETATE DIMEGLUMINE

Sponsor: BERLEX LABORATORIES, INC.

Approval Date: 02/28/96

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APPLICATION:

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter	X			
Final Printed Labeling				
Medical Review(s)	X			
Chemistry Review(s)				
EA/FONSI				
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology	X			
Biopharmaceutics Review(s)				
Bioequivalence Review(s)				
Administrative Document(s)	X			
Correspondence				

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Application Number: 019596/S08/S09

APPROVAL LETTER

DIY

FEB 28 1996

NDA 19-596/S-008, S-009

Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470-7358

Attention: Ms. Jacquelyn Hartley
Regulatory Administrator, Drug Regulatory Affairs

Dear Ms. Hartley:

We acknowledge your January 10, 1992, (S-009) supplemental new drug application received on January 13, 1992, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Magnevist[®] (brand of gadopentetate dimeglumine). This supplemental application provides for contrast enhancement and facilitation of visualization of extracranial head and neck lesions.

We acknowledge receipt of your amendments and correspondence dated July 30, 1992; June 29 and 30, and October 6, 1993; October 5, November 10 and 23, 1994; and February 10 and 17, 1995, for S-009. We further refer to our facsimile of January 11, 1994, containing draft labeling and our approvable letter for S-009 dated September 23, 1994.

We have completed the review of this supplemental application (S-009) including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, this supplemental application is approved effective on the date of this letter.

We also refer to your November 8, 1991, submission of the supplemental new drug application (S-008) for MRI contrast for visualization of lesions in the body (excluding the heart). This supplement was approved in our letter dated August 17, 1993. Additionally, we refer to our September 23, 1994, letter which reminded you that the promotion of breast imaging was not approved. We requested labeling revisions to further describe the body imaging indication. We refer to your responses dated November 10 and 23, 1994. We further refer to our meeting with you on November 17, 1994, to discuss the body imaging indication and the possibility of a breast imaging indication for Magnevist.

Part I of this letter will address the body imaging indication for supplement 008 and the language that is to be used for this indication. Part II will address supplement 009 labeling issues. The enclosure contains the final package insert language for both S-008 and S-009.

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Part I - BODY INDICATION

As discussed in our November 17, 1994, meeting, the FDA and Berlex have different understandings and recollections of the intent of previous meetings, telephone conversations, facsimiles, and agreements. Also, we view our requested labeling clarifications (e.g., our letter of September 23, 1994) from a different perspective. Nevertheless, we appreciate your willingness to offer alternative suggestions on labeling to address our regulatory concerns. We have seriously considered your comments and labeling proposals. These proposals were considered in conjunction with the pivotal data submitted for body imaging and whether the data would support inclusion of breast imaging in the body imaging indication.

As stated in our meeting of November 17, 1994, the pivotal trials in supplement 008 evaluated approximately 8-11 patients with Magnevist-enhanced breast MRIs. This is an insufficient database upon which to base an indication for breast imaging. Your submissions of November 10 and 23, 1994, noted that the database had 40 patients with breast imaging; these patients were not part of the original blinded database of pivotal trials submitted for efficacy. These patients were part of an open label study. Additionally, the pivotal trials were not designed to provide tissue confirmation, adequate sample size, or comparison to mammography. The data submitted do not provide information to assess the role of Magnevist-enhanced MRI as a screening test, an adjunct or alternative to mammography, or its use in detecting malignancy, cysts, implants, and other lesions. Therefore, these data do not support approval of the use of Magnevist for breast imaging.

The approval action dated August 17, 1993, for supplement 008 continues to be for the "use of Magnevist is for MRI contrast enhancement and facilitation of visualization of lesions in the body (excluding the heart)" and extends only to the body defined as intra-thoracic (excluding the heart) and intra-abdominal. We acknowledge that this may not have been implicit in the wording of the INDICATIONS section of the package insert subject to the August 18, 1993, approval of S-008. Therefore, the CLINICAL TRIALS and INDICATION sections should be revised as follows.

Label Revisions for the Body Imaging Indication

Labeling must be based upon adequate and well controlled data submitted as the basis for approval. The CLINICAL TRIALS section should include information from the pivotal trials.

CLINICAL TRIALS

[For the full CLINICAL TRIALS text, please see the attached final approved labeling].

"In two clinical trials, Magnevist for body imaging (intra-abdominal and intrathoracic, excluding the heart) was evaluated in MRI images from a total of 97 patients. Of these, 57/97 had intra-abdominal and 11/97 had intrathoracic lesions. The results of MRIs with and without Magnevist were compared blindly. After injection of Magnevist, additional

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lesions were identified in 32/97 (33%) of the patients; mean contrast enhancement (relative image intensity) increased from 1.58 to 2.11. The mean number of lesions before and after Magnevist were comparable (pre 1.49/patient, post 1.75/patient). Some lesions seen without Magnevist [9/97 (10%)] did not enhance with Magnevist; an additional 7/97 (8%) were not seen on post-Magnevist films. Overall, 41% of the post-Magnevist films provided increased contrast and 18% of the pre-Magnevist films had better contrast. Whether or not Magnevist can distinguish in the breast malignant and non-malignant tumors, cysts, dense tissue, and implants is not known. The doses for imaging intra-articular spaces, bone, and muscle soft tissue have not been studied."

INDICATIONS

In conclusion, we again appreciate your continued cooperation in the clarification of the labeling for supplement 008. The body imaging indication language should be revised immediately and, as noted in our letter of September 23, 1994, promotion for breast imaging should stop immediately.

If you wish to submit other data from adequate and well controlled studies for breast imaging, it will be considered. This information should be submitted as a new efficacy supplement for breast imaging. We encourage you to complete the protocol that was submitted on July 6, 1994, to study Magnevist for contrast enhancement in breast imaging. If there are any questions about this trial, we will be glad to discuss them.

PART II - SUPPLEMENT 009

This part of the letter addresses your proposed alternative language for labeling submitted in response to our September 23, 1994, approvable letter for supplement 009. Specifically, we refer to the itemized sections of the package insert which accompanied our letter and to your letters of November 10 and 23, 1994, providing detailed responses and subsequent changes.

We have completed our review of your comments and find them acceptable as modified below. With these changes (and other minor ones noted in the enclosed draft labeling), this supplement is approved effective the date of this letter. For your convenience, the major changes noted are identified with the item numbers used in your November 10, 1994, letter.

9. Pharmacokinetics

The essential point in your proposed additional paragraph on patients with renal impairment is already included in the preceding paragraphs. Therefore, the section should remain as it was, omitting the additional paragraph.

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10. CLINICAL PHARMACOLOGY (regarding protein binding).

We agree to the addition of your proposed sentence about an in-vitro protein-binding study; however, the statement on the lack of an in-vivo study is still needed. Thus, this paragraph should be revised to read:

"In-vitro laboratory results indicate that gadopentetate does not bind to human plasma protein. In vivo protein binding studies have not been done."

14. CLINICAL TRIALS

As noted in Part I of this letter, the CLINICAL TRIALS section is based upon the pivotal trial data upon which approval of Magnevist for body imaging was based. We note that your proposed revisions contain new language in paragraphs 4 and 5 which point to "differentiation from edema, differentiation from necrosis or ability to distinguish scar from disc", or to "affect on therapy", and "information on nodal disease". The trial design did not allow for verification of these findings; therefore, this information should be deleted. Also, this section should present the findings concisely. The total number of subjects must reflect the pivotal data sets used in the blinded image comparisons. (Phase 3 was comprised of 289 intracranial, 66 head and neck, and 97 body patient images. Major details on the trials used for the 1987 approval of the use of Magnevist for visualization of intra-cranial lesions are not necessary at this time.) This section must be revised as follows. The blanks are to be filled in based upon the pivotal trial denominators noted in the paragraphs.

"Magnevist® Injection was administered to 552 patients in clinical blinded image evaluation trials that studied the use of contrast enhancement in head and neck, brain and spine, and body (intra-abdominal and intrathoracic, excluding the heart). Of these 552 patients, _____ patients were between 18 and 59 years of age, and _____ patients were over 60 years of age; the mean age was _____ years (range _____). Of the _____ patients, _____ (____%) were male and _____ (____%) were female. The racial distribution was: Caucasian _____ (____%), Black _____ (____%), Hispanic _____ (____%), Asian _____ (____%), and other or unknown _____ (____%). Eligible patients had a reason for an MRI. Efficacy assessments were based on pre- and post-Magnevist film quality, film contrast, lesion configuration (border, size, and location), and the number of lesions. The protocols did not require specific diseases or histopathologic confirmation of findings.

In the clinical trials of Magnevist for head and neck MRI contrast enhancement, 66 patients received Magnevist 0.1 mmol/kg I.V. A total of 66 MRI images were evaluated blindly by comparing each pair of MRI images, before and after Magnevist. In these paired images, 56/66 (85%) had greater enhancement after Magnevist and 40/66 (67%) had better lesion configuration or border delineation

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after Magnevist. Overall, there was better contrast after Magnevist in 55% of the images, comparable enhancement in 44% before and after Magnevist, and better enhancement in 9% without Magnevist. Earlier, in similar trials, imaging studies of the central nervous system found that Magnevist significantly improved the ability to make a diagnosis.

In two clinical trials, Magnevist for body imaging (intra-abdominal and intrathoracic, excluding the heart) was evaluated in MRI images from a total of 97 patients. Of these, 57/97 had intra-abdominal and 11/97 had intrathoracic lesions. The results of MRIs with and without Magnevist were compared blindly. After injection of Magnevist, additional lesions were identified in 32/97 (33%) of the patients; mean contrast enhancement (relative image intensity) increased from 1.58 to 2.11. The mean number of lesions before and after Magnevist were comparable (pre 1.49/patient, post 1.75/patient). Some lesions seen without Magnevist [9/97 (10%)] did not enhance with Magnevist; an additional 7/97 (8%) were not seen on post-Magnevist films. Overall, 41% of the post-Magnevist films provided increased contrast and 18% of the pre-Magnevist films had better contrast. Whether or not Magnevist can distinguish in the breast malignant and non-malignant tumors, cysts, dense tissue, and implants is not known. The doses for imaging intra-articular spaces, bone, and muscle soft tissue have not been studied."

In similar studies, in the brain and spinal cord, Magnevist 0.1 mmol/kg I V provided contrast enhancement in lesions, with an abnormal blood brain barrier.

15. INDICATIONS AND USAGE:

The INDICATIONS AND USAGE section for CNS imaging is consistent with language already in use for other agents of this class. Your proposed term "surrounding tissues" could mean bone, as well. Magnevist-enhanced contrast in bone was not studied in pivotal clinical trials. Regarding the pediatric language of "over 2 years of age" versus "2 years and older", the language must be consistent with study data and with the "Requirements on the Content and format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling; Final Rule" (FR 64249 dated December 13, 1994)[21 CFR 201.57(f)(9)(I-iv)]. Since the data were derived from older patients, you must revise the statement accordingly, "children 2 years up to 16 years." Further revision will depend on future development of Magnevist in children and adolescents.

The INDICATIONS AND USAGE section must be revised to read:

"Magnevist is indicated for contrast enhancement of Magnetic Resonance Imaging (MRI) as follows:

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Central Nervous System

Magnevist is indicated for use in MRI in adults and children (2 years up to 16 years) to visualize lesions with abnormal blood-brain barrier vascularity in the brain (intracranial lesions), spine, and associated tissues.

Extracranial /Extraspinal Tissues

Magnevist is indicated for use in MRI in adults to facilitate the visualization of lesions with abnormal vascularity in the head and neck

Body (Intrathoracic [excluding the heart]/Intra-abdominal)

Magnevist is indicated for use in MRI in adults to facilitate the visualization of lesions with abnormal vascularity in the body [intrathoracic (excluding the heart)/intra-abdominal] regions."

18. WARNINGS - Explanation of the term "hypersensitivity-like"

You requested a clarification of our use of the term "other hypersensitivity-like disorders". This term is used to remind physicians to consider disorders that are not allergies but which could have similar manifestations; e.g., autoimmune disease, systemic mastocytosis, some immunodeficiencies, etc.. This or similar wording is consistent with other imaging agent labeling. This paragraph must remain as is.

21. PRECAUTIONS (General) - Fourth paragraph

We have considered your alternative to paragraph 4. While it is technically correct, it requires clarification and must be based on submitted data. This paragraph must be revised to read as follows:

"Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function. Magnevist is not significantly eliminated by the hepatobiliary enteric pathway, but it is dialyzable (See Pharmacodynamics Section). Caution should be exercised in patients with either renal or hepatic impairment."

24. Regarding the inclusion of transaminases in the LABORATORY TEST FINDINGS section.

The current version of the package insert contains a sentence which reads "Transitory changes in serum iron and bilirubin levels have been reported in patients with normal and abnormal liver

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function (see PRECAUTIONS - General)." Our request was to add "transaminase levels" to this sentence. The data you submitted on November 10, 1994, provided several tables which demonstrate inconsistent changes in transaminase levels. Therefore the phrase must be added.

26. PREGNANCY CATEGORY C

We accept the addition of the word "slightly" to modify the fetal development statement. The dosing information needs to be further clarified as follows:

"Gadopentetate dimeglumine retarded fetal development slightly when given intravenously for 10 consecutive days to pregnant rats at daily doses of 0.25, 0.75, and 1.25 mmol/kg (2.5, 7.5, and 12.5 times the human dose based on body weight) and when given intravenously for 13 consecutive days to pregnant rabbits at daily doses of 0.75 and 1.25 mmol/kg (7.5 and 12.5 times the human dose respectively based on body weight) but not at daily doses of 0.25 mmol/kg. Congenital anomalies were not noted in rats or rabbits.

Adequate and well controlled studies have not been conducted in pregnant women. MAGNEVIST® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED

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LABELING" for approved supplemental NDAs 19-596/S-008, S-009. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mr. Santford Williams, Consumer Safety Officer, at (301) 443-1560.

Sincerely yours.

/S/

**APPEARS THIS WAY
ON ORIGINAL**

Patricia Y. Loxe, M.D., M.B.A.
Director, Division of Medical Imaging
and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Final draft labeling dated 2.14.96

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cc:

Original NDA 19-596
HFD-160/Div. files
HFD-161/CSO/S.Williams
HFD-160/Meyers/Melograna/Ju
HFD-713/Smith
HFD-426/Stevens
HFD-100
DISTRICT OFFICE
HF-2/medwatch (with labeling)
HFD-80 (with labeling)
HFD-240/S.Sherman (with labeling)
HFD-613 (with labeling - Only for applications with labeling.)
HFD-735/D.Baresh (with labeling-for adverse reaction changes only)

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drafted: RB/July 24, 1995/19596.004
revised:P. Love/ 12.8.95
revised:BCollier/12.14.95
r/d:Cheever/12.14.95
revised: P. Botstein/ 1.22.96
r/d: S. Williams/ 1.24.96
revised:Cheever/2.12.96
final: Cheever/2.14.96/N19596ap.S09

APPROVAL (S-009)

/S/ 2/14/96
2/26/96
/S/

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

APPROVABLE LETTER

NDA 19-596/S-009

SEP 23 1994

Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, New Jersey 07470-7358

Attention: Ms. Jacquelyn Hartley
Regulatory Administrator, Drug Regulatory Affairs

Dear Ms. Hartley:

Reference is made to your supplemental new drug application S-009 dated January 10, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Magnevist Injection (brand of gadopentetate dimeglumine).

Supplement 009 provides for the use of Magnevist[®] for contrast enhancement and facilitation of visualization of extracranial head and neck lesions in patients who are undergoing magnetic resonance imaging. We acknowledge receipt of your amendments and correspondence dated July 30, 1992; and June 30 and October 6, 1993.

We also refer to our approval letter for supplement 008, dated August 17, 1993. Supplement 008 provided for the use of Magnevist in MRI for contrast enhancement and facilitation of visualization of lesions in the body (excluding the heart). Additionally, we refer to the meeting between you, the Division of Drug Marketing, Advertising, and Communications (DDMAC), and this Division on September 23, 1993. In that meeting you were advised that promotion for breast imaging was not approved because of inadequate patient sample size and the lack of method validation. Also, the magnetic resonance imaging devices are not approved for imaging the breast. Therefore, this Division and DDMAC requested that Berlex delete specific claims regarding breast imaging from their promotion of Magnevist. We have been advised that subsequent to the meeting, DDMAC reviewed an October 5, 1993 version of your advertising which included a breast diagram and found it to be generally acceptable. Nevertheless, in the September 23, 1993, meeting, you were also advised that final promotion of supplement 008 should await agreement on the package insert revisions in the **CLINICAL TRIALS** and **INDICATIONS** sections. By previous agreement this was to occur with the action on supplement 009. On January 11, 1994, draft labeling was sent by facsimile to you.

We have completed our review of supplement 009 as amended including the draft labeling dated October 6, 1993, and it is approvable. Before this application may be approved, however, we request that you submit the following labeling revisions. These revisions include changes for both supplements 008 and 009. Please note that the labeling revisions do not address labeling that was not specifically submitted to these pending supplements. These revisions are a condition of approval for supplement 009.

Effective upon receipt of this letter, the promotion of supplement 008 is expected to immediately comply with the portions of this labeling which affect the body indication as discussed in our September 23, 1993 meeting (i.e, the Clinical Trials, Indication, Dosage and Administration and related Precautions section changes). Current labeling for supplement 008 must be revised as described below. If these changes are not implemented within 60 days or the next printing, the product may be considered misbranded.

The required labeling revisions are as follows:

1. The first paragraph under **DESCRIPTION** should be revised to read:

MAGNEVIST[®] (brand of gadopentetate dimeglumine) Injection is the N-methylglucamine salt of the gadolinium complex of diethylenetriamine pentaacetic acid, and is an ionic injectable contrast medium for magnetic resonance imaging (MRI). MAGNEVIST[®] Injection is provided as a sterile, clear, colorless to slightly yellow aqueous solution in vials for intravenous injection.

2. The second paragraph under **DESCRIPTION** should describe the chemical composition and structure of MAGNEVIST[®] Injection (currently the fourth paragraph of the approved labeling).
3. The third paragraph under **DESCRIPTION** should describe the formulation of MAGNEVIST[®] Injection (currently the second paragraph of the approved labeling).
4. The fourth paragraph under **DESCRIPTION** should indicate the pH of MAGNEVIST[®] Injection and introduce the physicochemical data (currently the fifth paragraph of the approved labeling).
5. Under **PARAMETER** under **DESCRIPTION**, please indicate at what temperature the density is 1.195 g/mL. Also, please provide values for the octanol:H₂O coefficient and the specific gravity of MAGNEVIST[®] Injection.

6. Please revise the last paragraph under **PARAMETER** to read:

MAGNEVIST[®] Injection has an osmolality 6.9 times that of plasma which has an osmolality of 285 mOsmol/kg water and is hypertonic under conditions of use.
7. Please add the parenthetical element "(General)" after the heading of **CLINICAL PHARMACOLOGY**.
8. Immediately under the heading of **CLINICAL PHARMACOLOGY**, please insert the subheading of **Pharmacokinetics**.
9. In the third paragraph under **Pharmacokinetics**, please substitute the word "renal" for "urinary".
10. Please delete the fourth paragraph under **CLINICAL PHARMACOLOGY** and add the following paragraph:

It is unknown if protein binding of MAGNEVIST[®] occurs in vivo.
11. After the fourth paragraph under **CLINICAL PHARMACOLOGY** (see #10), please insert the subheading of **Pharmacodynamics**.
12. Please add the following sentence to the end of the third paragraph under **Pharmacodynamics**:

The pharmacokinetic parameters of Magnevist in various lesions are not known.
13. Please delete the fourth paragraph under **Pharmacodynamics**.
14. Please add the heading of **CLINICAL TRIALS** following the third paragraph under **Pharmacodynamics**. Under this heading, please add the following text [Your original submission included demographics for the unblinded trials but not the blinded re-read. Therefore, in your response, please include a separate table which justifies the numbers that will be inserted in the text.]:

Two open label, randomly selected, blinded read datasets of patients with a variety of indications for MRI of the thorax and abdomen were evaluated. A total of ___ subjects were entered (___ men, ___ women) with a mean age of ___ (range ___ to ___). The trials compared pre- (non-contrast) and post-Magnevist MRI images for film quality, determination of lesion configuration (border, size, location), and number of lesions. The film contrast scores and quality (no contrast, equivocal, good, excellent) were also compared. A confirmation of the findings or resolution of pre- and post-Magnevist differences was not done in all patients.

Based upon these data, additional information on lesion configuration was identified in 32/97 (33%) of the images, and the mean contrast enhancement increased from 1.58 to 2.11. The mean number of lesions pre- and post-Magnevist were comparable (pre 1.49, post 1.75). Also in these data, 4/97 (4%) of the images were lost. Some lesions seen on pre-Magnevist MRI, 9/97 (10%), did not enhance with Magnevist, and 7/97 lesions (8%) were not seen on post-contrast films. Overall, 41% of the post-Magnevist films provided increased contrast while 18% of the pre-Magnevist films had better contrast. These findings were not verified and clinical relevance is not known.

Two open label, blinded reader datasets of subjects with an indication for an extracranial head and neck scan were evaluated in a total of ___ subjects (___ males; ___ women) whose mean age was ___ (range ___ to ___). Subjects received Magnevist in a dose of _____. The non-contrast and Magnevist MRI images were evaluated for film quality, determination of lesion configuration (border, size, location), and number of lesions. The film contrast scores and quality (no contrast, equivocal, good, excellent) were also compared. A confirmation of the findings was not done on all patients.

Of the ___ patients, 66 film sets were evaluated for enhancement. Of these film sets, 56/66 (85%) of the post-contrast images were enhanced. Of the post-contrast images, 40/66 (67%) demonstrated better lesion configuration or border; however, in 5 (8%) of the images, the lesion enhancement was better on pre-contrast MRI. Overall, there was more contrast after Magnevist in 55% of the scans, comparable contrast before and after Magnevist in 44% of the scans, and better contrast without Magnevist in 9% of the scans. The data on auditory and ocular MRI images is limited. Staging of disease and tissue confirmation was not performed.

15. Please delete the current language under **INDICATIONS AND USAGE** and substitute the following language:

Magnevist is indicated for contrast enhancement of Magnetic Resonance Imaging (MRI) as follows:

Central Nervous System

Magnevist is indicated for use in MRI in adults and children (over 2 years of age) to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine, and associated tissue.

Extracranial/Extraspinal Tissues

Magnevist is indicated for use in MRI in adults to facilitate the visualization of lesions with abnormal vascularity in the head and neck.

Body (Intrathoracic [excluding heart]/Intraabdominal)

Magnevist is indicated for use in MRI in adults to facilitate the visualization of lesions with abnormal vascularity in the body (intrathoracic [excluding heart]/intraabdominal).

Magnevist is **not** indicated for visualization of the heart or the breast.

16. Under **WARNINGS**, please substitute the word "by" for the first use of word "in" in the first sentence.
17. In the third paragraph under **WARNINGS**, please insert the phrase "in a supine position" following the word "observed" in the last sentence.
18. Please insert the following language as a fourth paragraph under **WARNINGS**:

Patients with a history of allergy, drug reactions, or other hypersensitivity-like disorders should be closely observed during the procedure and for several hours after drug administration. (See **PRECAUTIONS (General)**)

19. Under **PRECAUTIONS (General)**, please add a new paragraph just before the existing paragraph on seizure. The text should be as follows:

MRI WITH MAGNEVIST CONTRAST ENHANCEMENT MAY IMPAIR THE VISUALIZATION OF EXISTING LESIONS. SOME OF THESE LESIONS MAY BE SEEN ON UNENHANCED, NON-CONTRAST MRI. THEREFORE, CAUTION SHOULD BE EXERCISED WHEN CONTRAST ENHANCED SCAN INTERPRETATION IS MADE IN THE ABSENCE OF A COMPANION UNENHANCED MRI.

20. Under **PRECAUTIONS (General)**, please use the singular word "seizure" in the second paragraph.

21. Please revise the third paragraph under **PRECAUTIONS (General)** to read as follows:

Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function. Based on a renal impairment study in rats, it appears that Magnevist is not significantly eliminated by the hepatobiliary enteric pathway even when both kidneys are occluded. Therefore, caution should be exercised in patients with either renal or hepatic impairment.

22. Please revise the fourth paragraph under **PRECAUTIONS (General)** to read as follows:

The possibility of a reaction, including serious, life-threatening, or fatal anaphylactic or cardiovascular reactions or other idiosyncratic reactions (see **ADVERSE REACTIONS**), should always be considered, especially in those patients with a history of a known clinical hypersensitivity or a history of asthma or other allergic respiratory disorders.

23. Please revise the remaining paragraphs after the fifth paragraph under **PRECAUTIONS (General)** to read as follows:

Diagnostic procedures that involve the use of contrast agents should be carried out under the direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

When MAGNEVIST[®] Injection is to be injected using nondisposable equipment, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. After MAGNEVIST[®] Injection is drawn into a syringe, the solution should be used immediately.

Repeat Procedures: Data for repeated procedures are not available. If in the clinical judgment of the physician sequential or repeat procedures are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

Repeat Injections: (See **DOSAGE and ADMINISTRATION**)

Information for Patients:

Patients scheduled to receive MAGNEVIST[®] Injection should be instructed to inform their physician if the patient:

1. Is pregnant or breast feeding.
 2. Has any blood disorders; i.e., anemia, hemoglobinopathies, or diseases that affect red blood cells.
 3. Has a history of renal or hepatic disease, seizure, asthma or allergic respiratory disorders.
24. Under **LABORATORY TEST FINDINGS**, please revise the sentence to read as follows:
- Transitory changes in serum iron, bilirubin, and transaminase levels have been reported in patients with normal and abnormal liver function (See **PRECAUTIONS (General)**).
25. Under **CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY**, please add the phrase "or potential effects on fertility" to the end of the first paragraph.
26. Under **PREGNANCY CATEGORY C** in the first paragraph, please state the length of time (in days) that the doses were administered.
27. Please revise the first paragraph under **ADVERSE REACTIONS** to describe the number of patients in the safety database (please see the enclosed labeling).
28. Please revise the second paragraph under **ADVERSE REACTIONS** to read as follows:
- The following additional adverse events occurred in fewer than 1% of the patients:
29. Please delete the last paragraph under **ADVERSE REACTIONS** concerning laboratory values.
30. Under **DOSAGE AND ADMINISTRATION**, please add the phrase "in accordance with regulations dealing with the disposal of such materials" to the end of the last sentence of the first paragraph.

31. Under **HOW SUPPLIED**, please insert the phrase "in rubber stoppered vials" at the end of the first sentence in the first paragraph. Also, please delete the phrase "rubber stoppered" from each of the size descriptions.
32. Under **STORAGE**, please revise the third sentence in the first paragraph to read:

Should freezing occur in the vial, MAGNEVIST[®] Injection should be brought to room temperature before use.
33. Under **STORAGE**, please add the following sentence to the end of the first paragraph:

Should solids persist, discard vial.

The revisions noted above have been incorporated into the enclosed draft labeling prepared by the Division. Double underlined text in the draft labeling indicates new text, and underlined areas indicate the space where additional text will need to be inserted.

We request that as per our previous discussions, you will further revise the **CLINICAL TRIALS** section to reflect relevant data from your existing indications. This should be completed within 12 months of receipt of this letter. This revision may be accomplished post-approval of Supplement 009.

As a condition of approval, we also request that you commit to undertake the following Phase 4 trials to:

Protocols for Phase 4 commitments should be submitted for review prior to their implementation.

Please note that any further studies on new doses, regimens, or indications of Magnevist will continue to require a full assessment of safety and efficacy.

Within 10 days after the date of this letter, you are required to amend the application or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application. The changes indicated above cannot be legally implemented until you have been notified in writing that the application is approved.

Sincerely yours,

/S/

Patricia Y. ~~Love~~, M.D., M.B.A.
Director
Division of Medical Imaging,
Surgical and Dental Drugs
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Revised labeling dated September 16, 1994

**APPEARS THIS WAY
ON ORIGINAL**

CC:

NDA ARCH
HFD-160/DIVFILE
HFC-130/District Office
HFD-160/Jones/Ju/Sheinin/Salazar/Bailey/Melograna/Cooney/Greenman
HFD-160/Love
HFD-161/Blay *78 9/21/94*
Acknowledgements: Cheever, 9.12.94; Love, 9.13.94
F/T by: CWilson, 9.14.94

SUPPLEMENT APPROVABLE

/S/

9/21/94

✓
**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

MEDICAL REVIEW(S)

DIV
FEB 10 1995

DIVISION OF MEDICAL IMAGING, SURGICAL AND DENTAL DRUG
PRODUCTS
MEDICAL IMAGING GROUP

ADDENDUM to NDA #19, 596, S-009 June 28, 1995
(Responses to Dr. Jones' questions)

M.O.: H. W. Ju, M.D.

NDA 19,596, S-009
Magnevist (Gd-DTPA)

Document Date: Feb 10, 1995

Berlex Laboratories, Inc.
Wayne, NJ 07470-7358

Literature references:

The 6 articles provided by the sponsor was reviewed by this reviewer and it is concluded as follows:

- (1) Magnevist is dialyzable.
- (2) At the third dialysis, 5% of the initial concentration of Magnevist will remain in the plasma
- (3) Fecal excretion of Magnevist is minimal
- (4) Theoretically, to remove Magnevist from plasma completely, it will require 3.5-4.2 hours at a plasma flow rates of 300 cc/min
- (5) Patient with severe renal impairment (creatinine clearance <20 ml/min), excretion of Magnevist may be less complete; therefore, hemodialysis should be considered.
- (6) Long term stability in the serum is not known
- (7) There is a conflict in pediatric GFR data between Rowland (presented by the sponsor) and Aperia (Clin. Perinatal).

Reviewer's comment: The sponsor should verify the above results by performing the appropriate Phase 4 trials

Copy of this NDA supplement is being sent to Pharmacokinetic Division for review. Statistical reviewer was completed on 2/17/95. (see attached)

/S/

H. W. Ju, M.D.

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No test - Assent review complete
1
/S/ 7/1/95

Encl:

- (1) NDA 19,596, S-009, MOR
- (2) Statistical reviewe and evaluation
- (3) Annual report: October, 1991

IBM:MAGNV-NS-AD9

**APPEARS THIS WAY
ON ORIGINAL**

OK APR 18 1995

DIVISION OF MEDICAL IMAGING, SURGICAL AND DENTAL DRUG
PRODUCTS
MEDICAL IMAGING GROUP

MEDICAL OFFICER'S REVIEW

H. W. Ju, M.D.

NDA 19-596, S-009
Magnevist
Supplemental application
(Revised Drug Labeling)

Date submitted: Feb. 17, 1995
Date received: Feb. 21, 1995
Date assigned: Feb. 22, 1995
Date completed: Mar. 7, 1995

APPLICANT

Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470-7358

This drug labeling review is in reference to the Sponsor's reply to the supplement (009) dated November 10, 1994. Present submission provided certain answers to the above review (Questions 9, 21, 24 and 27).

Question 1: The word is "ionic", i.e., Magnevist is an ionic contrast medium. There is no difference in safety and efficacy between the ionic MR agent (Magnevist) and nonionic MR agents (Ominiscan and ProHance).

Questions 2-8: No comment

Question 9: The sponsor's statement is true; however, it is promotional. (see present submission question 9. This section needs to be reviewed by **pharmacologist.**) — PHARMAKINETICISTS

Question 10: Please refer to **Pharmacology.**

Questions 11-13: No comment

Question 14: The sponsor should provide information as requested by Dr. Love; i.e., data derived from original NDA (Brain and spine for adults and children), head and neck and total body.

Question 15: This reviewer prefers to keep the original wording. **Presently this section is under discussion.**

Question 16: No comment



Question 17: The phrase "in a supine position" should be kept as specified. The sponsor's data are correct. However, for the few patients who will develop hypotension after the drug administration, it will be safer to observe these patients in a supine position regardless if it is drug related.

Question 18: The closely related interpretation for "Hypersensitivity-like disorders" is "Pseudo-allergic reactions".

The following two paragraphs are obtained from page 254, chapter 8, Pharmaceuticals in Medical Imaging. by D. P. Swanson, H. M. Chilton and J. H. Thrall, Macmillan Publishing Col., Inc. New York, 1990:

"Many terms have been used in the radiological literature in referring to "unpredictable" reactions. These terms include "idiosyncratic," "anaphylactoid," "allergic," "pseudo-allergic," "generalized" reactions. The variability in terminology is largely a reflection of incomplete and evolving knowledge of the etiology of the unpredictable reactions. ...

"Perhaps the best general qualifying term for the majority of unpredictable reactions to contrast media is "pseudo-allergic." Pseudo-allergic reactions may have entirely similar clinical manifestations as true allergic reactions. The term implies that the initiating event does not involve a reaction with a drug-specific antibody, but can still involve activation of one or more immunologic effector systems by another mechanism".

Hypersensitivity-like reactions are also used in several publications (Medline).

Question 19: Berlex may use the phrase "As with any paramagnetic contrast agent", since similar cases were reported with the administration of ProHance. *Agree Ref.*

Question 20: No comment

Question 21: The sponsor's statement is correct. However, the original sentences as recommended should be kept in order to provide an ~~uniformed~~ description among the three Gd compounds.

Question 22: No comment

Question 23: No comment

Question 24: The sponsor was correct. In the NDA review, serum iron and bilirubin were affected by Magnevist injection; however, liver enzymes were not affected by Magnevist administration. *Agree Ref.*

Question 25: **Refer to Pharmacology**

Question 26: Refer to Pharmacology

Question 27: The sponsor's presentation is correct. The data base was obtained from the following five trials: Original NDA (adult brain) and Supplements 001, 005, 008 and 009 (Spine, Pediatric, Whole body and Head and Neck respectively. See attached submission)

Questions 28-32: No comment

/S/

H. W. Ju, M.D.

3/7/85

Group leader's comments:

- Regarding question #21: The sponsor's lengthy labeling change is unnecessary although reasonable. I agree with Dr. Ju's advice to maintain Dr. Loven's version as noted in question #21.
- In regard to question #9: The sponsor was requested to change the word "unnary" in paragraph 3 under Pharmacokinetics to "renal". That change alone is sufficient.
- Question #25: Studies of Magnovist for "potential effects on fertility" have been conducted according to the sponsor and if those facts are true they should be included (as worded by the sponsor) in the package insert.
- Question #10 - I concur with the sponsor + find data in submission dated 7/23/94 pgs. 673+674 Vol 21.2 (Annual Report #5) agree - "gadopentstate does not bind to human plasma proteins".
- Question #26: I agree with the sponsor's recommended labeling.

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/S/

A. E. Jones, M.D.

3/16/95

cc: NDA 19,596
 HFD-160/Division File
 HFD-160/MO: H.W.Ju
 HFD-160/CSO: S.Lange
 HFD-160/Che: M.Salazar
 HFD-160/Mic: P.Cooney
 HFD-160/Pha: S.Wilson
 R/D Init. by A.E.Jones
 IBM: MGNVST2.LAB

Note: Also need PK to review # 9+10. Return to me when completed.
 /S/ 4/18/95

DIY
MAR 21 1995

DIVISION OF MEDICAL IMAGING, SURGICAL AND DENTAL DRUG
PRODUCTS
MEDICAL IMAGING GROUP

M.O.: H. W. Ju, M.D.

NDA 19,596, S-009
Magnevist (Gd-DTPA)

Document Date: Feb 10, 1995
Date Received: Feb 13, 1995
Date Assigned: Feb 15, 1995
(received on Feb 24, 1995)
Date Completed: Jun 11, 1995

Phase 4 trials

Berlex Laboratories, Inc.
Wayne, NJ 07470-7358

FDA letter dated September 23, 1994 requested the sponsor to respond the following issues:

- (1) Drug labeling changes
- (2) Phase 4 studies

Drug labeling changes were answered by the sponsor on November 10, 1994 and our Division is preparing to respond accordingly.



The sponsor presented the following tables by using the data derived by (1) all Phase 2 and 3 US clinical trails (2054 subjects) and (2) controlled Phase 2 and 3 US clinical Trials included in original and supplemental NDAs (1113 subjects).

(1) **EVALUATION AND DEVELOPMENT OF DOSE ADJUSTMENTS FOR AGE, WEIGHT AND GENDER.** (pages 1-11)

Adverse events by age

All Phase 2 and 3 US clinical trials (2050 subjects)

Trials	All ages(yrs)	<18 yrs	18-64 yrs	≥65 yrs
All trials	Total N=2049	N=112(%)	N=1616(%)	N=321(%)
At least 1 AE	285(13.9)	7(6.3)	231(14.3)	47(14.6)
Controlled trials*	Total N=1113	N=105(%)	N=804(%)	N=204(%)
At least 1 AE	181(16.3)	7(6.7)	138(17.1)	36(17.6)

* Brain (original NDA), Spine (S-001), Pediatric (S-005), Body (S-008) and H & N (S-009).

Headache was the most common AE

Post-marketing experience (U. S. 1990 subjects)

The above data were derived from practitioners and US and those recorded in the literature. There were a total of 140 reported AD in Europe; however, due to the lack of foreign sales distribution data, these 140 AE are not included in this analysis. There was a total of 1850 AEs which are groups by age as below:

Age (Years) by decade	No. of patients with AEs	
Age <u>mission</u>	115	6.2%
< 10	31	1.8%
11-20	82	4.4%
21-30	240	13.0%
31-40	429	23.1%
41-50	387	20.9%
51-60	241	13.0%
61-70	197	10.6%
≥ 71	128	6.9%
Total	1850	

Pediatric data from spontaneous, post-marketing reports

There were a total of 5 serious AEs since Magnevist initially entered the US market (3 in US and 2 in foreign sources) and one nonserious AE.

Adverse events by weight

All Phase 2 and 3 US clinical trials (2054 subject)

Weight (kg)	≤39	40-59	60-79	80-99	≥100
All trials					
Total N=2054	N=71(%)	N=417(%)	N=909(%)	N=552(%)	N=105(%)
At least 1 AE	5(7.0)	51(12.2)	130(14.3)	83(15.0)	16(15.2)
Controlled trials					
Total N=1113	N=64(%)	N=230(%)	N=484(%)	N=285(%)	N=50(%)
At least 1 AE	4(4.6)	35(15.2)	78(16.10)	54(18.9)	10(20.0)

Headache was the most common AEs.

Adverse events by gender

	Gender	Male	Female
All trials			
Total N=2054		N=1081(%)	N=973(%)
At least 1 AE		150(13.9)	135(13.9)
Controlled trials			
Total N=1113		N=604(%)	N=509(%)
At least 1 AE		109(18.0)	N=509(14.1)

Headache was the most common AEs.

Post-marketing experience (1990 patients)

The following reported AEs include reports by practitioners, US or foreign patients, and those recorded in the literature.

Age (Years) by Decade	Total	Male N(%)	Female N(%)	Gender not indicated
Age missing	115	47(41)	61(53)	7
≤10	31	18(58)	13(42)	0
11-20	82	36(44)	46(56)	0
21-30	240	107(45)	133(55)	0
31-40	429	181(42)	247(58)	1
41-50	387	171(44)	216(56)	0
51-60	241	92(38)	148(62)	1
61-70	197	88(45)	106(55)	3
≥71	128	43(34)	85(66)	0
Total	1850	783(42)	1055(57)	12

Sponsor's conclusion

The sponsor concluded as follows:

After evaluating the safety data from all Phase 2 and 3 US clinical trials and post-marketing experience, Berlex Laboratories, Inc. concludes that there are no safety concerns with regard to age, weight or gender. Therefore, further evaluation of dose adjustments for these demographic parameters is not needed."

Reviewer's comments

- (1) The reviewer agrees with FDA statistical review that the this limited evidence suggests several potential correlations with fewer adverse events for smaller, younger or female patients. Prospective safety studies would be necessary to confirm these suggested correlations.
- (2) In reference to the pediatric patient group, in the introduction section of this submission (page 1, paragraph 4), the sponsor made the following statement:

"Because the GFR is known to vary with age in children, the clearance of any drug such as Gd-DTPA that is excreted exclusively by glomerular filtration is also expected to vary in children (Rowland M and Tozer T. Clinical Pharmacokinetics: Concepts and Applications, 2nd edition, Philadelphia, PA; Lea & Fabiger; 1989, 222-237). Except for neonates (up to 2 months), Gd-DTPA clearance in pediatric populations is predicted to exceed that found in adults. In neonates, the clearance of Gd-DTPA is expected to be 70% of the clearance in normal adults. Clearance of Gd-DTPA is predicated to be maximum in infants (2 months to 1 year): 240% of the adult value. With increasing age, the clearance of Gd-DTPA is expected to decrease in the pediatric population, and approach that of adults

After administration of Gd-DTPA to pediatric subjects, the plasma concentration of Gd-DTPA may decline more rapidly compared to that in adult subjects."

Contrary to the sponsor's above description, this reviewer obtained the following references for further information:

Contrast media: "The pediatric radiologist is frequently called upon to evaluate the urinary tract in the neonatal infant and on many occasions this will be done during the first few days of life. It is at this time when important decisions have to be made that excretion urography often fails to provide the necessary answer because of the infant's renal physiology. At first the normal newborn's glomerular filtration rate is only approximately 21 per cent that of a normal adult. By the third day of life it has increased to 30 per cent and between one and two weeks has more than doubled to 44 per cent of the adult value. As the opacity of the urogram depends on the product of the glomerular filtration rate and plasma concentration, the reason for increased failure rate of excretion urography during the first phase of life is easily apparent. The child's clinical condition (e.g., vomiting) may aggravate this situation even further." (Evaluation of the Urinary Tract in the Neonatal Period, DJ Martin, et al, Radiologic Clinics of North America, Vol XIII, No. 2, August 1975, page 359)

Glomerular Filtration Rate (Aperia A, Zetterstrom R: Renal control of fluid homeostasis in the newborn infant. Clin. Perinatal 9:523-533, 1982)

Age	ml/min/1.73 m ²
Term Newborn	23
Neonate	
4-7 Days	34
8-12 Days	50
15-30 Days	54
2 Months	69
3 Months	71
4 Months	88
6 Months	110

Reviewer's comment

Rowland's data and Aperia's data are different especially at neonate and young infant groups. The sponsor should investigate the discrepancy.

- (2) DEVELOPMENT OF DOSE ADJUSTMENTS FOR PATIENTS WITH RENAL AND/OR LIVER IMPAIRMENT (pages 12-35)

Renal impairment

The sponsor presented data from the following two studies:

(a)

The trial was to evaluate the tolerance and pharmacokinetics of Magnevist after single I.V. injection in patients with and without impaired renal function. Twenty-four (24/27) patient completed MRI. Three (3/24) patients had normal renal function ($GFR \geq 80$ mL/min) and 21 had impaired renal function ($GFR < 80$ mL/min). Depending on degree of renal impairment, total and renal clearance of Gd-DTPA ranged _____ respectively.

The half life of the terminal disposition phase varied with the renal function and ranged _____ in these patients. The volume of distribution was independent of renal function in these patients. The average recovery of Gd-DTPA in urine was $92(\pm 13)\%$ of the dose. In feces, only _____ of the dose were recovered. There was a highly significant linear correlation between total clearance of Gd-DTPA and creatinine clearance.

The sponsor concluded the Gd-DTPA at a dose of 0.1 mmol/kg body weight showed good renal tolerance in all patients with and without preexisting renal impairment. Even in patients with severe impairment of renal function, there was no increase of serum creatinine after Gd-DTPA. In patients with renal failure requiring dialysis, Gd-DTPA can be easily eliminated by hemodialysis. Therefore impaired renal function or renal failure is no contraindication for the use of Gd-DTPA.

Reviewer's comment

This submission is inadequate. This is only a synopsis of part of foreign studies. The data were not well analyzed nor submitted. If the sponsor would like to use this study (rather than conducting new studies), detailed evaluations including statistical analysis must be conducted.

(b)

The trial was to evaluate the effects of Magnevist at 0.1 mmol/kg in a double-blind, placebo controlled, crossover study in renally impaired subjects. A total of 25 patients with various degrees of renal impairment were enrolled in this study; however, only 16 patients completed the study. 10 AEs were reported by 4 patients after Magnevist injection (i.v. line hemorrhage, pain, warmth, numbness, coldness, weakness, tired, headache, GI distress and urine abnormality). AEs were reported by 5 patients who received placebo (weakness, warmth, postural hypotension, dizziness, pruritus, and taste abnormality).

The sponsor concluded that Magnevist had no effect on serum BUN or creatine levels nor any effect on other serum chemistry tests, hematology tests, vital signs or physical examination. Magnevist was well tolerated. In normal and renally impaired subjects, Gd-DTPA was excreted unchanged in the urine by the process of glomerular filtration.

Reviewer's comment

The above trial was evaluated by this reviewer on Feb. 22, 1993 (Date of submission: August 26, 1992). The reviewer concluded that the study was incomplete for iron metabolism in patients with renal insufficiency and a repeated study was suggested. However, since the drug labeling was not changed then, follow up studies were recommended.

Hepatic impairment

The sponsor stated that clinical studies in normal and renally impaired subject showed that biliary excretion plays an insignificant role in the disposition of Gd-DTPA. A very small portion (<0.4%) of the intravenously administered Gd-DTPA was excreted in the feces. In subjects with severe renal impairment (creatinine clearance <40 mL/min), the fecal excretion was comparable to the patients with normal renal function (6). Therefore, impaired liver function will not alter the pharmacokinetic properties of Gd-DTPA. (page 15)

The effect of Magnevist on hepatic function was examined by liver function tests (alkaline phosphatase, SGPT, SGOT, and total bilirubin). These parameters were measured at 2-4 hours, 24 hours, 48 hours and 72 hours.

The following analyses were performed on data from the 1393 of 2054 patients in all US Phase 2 and Phase 3 clinical studies.

- (a) Number of patients with transitions from pre-injection to post-injection values relative to the normal ranges, (i.e., N/L-normal to low, N/H - normal to high, L/H - low to high, H/L - high to low, etc).
- (b) Number of patients with $\pm 1/3$ change relative to the normal range, from pre-injection to post-injection.
- (c) Number of patient with ± 15 change post-injection, from the pre-injection value.
- (d) The number of patients with transitions from pre-injection based on multiples of the upper limit of the normals ranges (see reviewer's comments).

Reviewer's comment

The above methods of analyses appears very impressive. However, if the number of patients with pre-contrast abnormal liver function tests is analyzed, the total number of the patients is small. The reviewer composed the following table:

Alkaline phosphatase

The normal range is 20-150 IU/L

There was a total of 9 patients who had value less than 20 IU/L.

There was a total of 128 patients who had value greater than normal at 2-4 hours, 24 hours, 48 hours or 72 hours.

2N - 84 patients have value greater than 1X but less than or equal to 2X the upper limit of the normal range

3N - 31 patients had value greater than 2X but less than or equal to 3X the upper limit of the normal range

4N - 7 patients had value greater than 3X but less than or equal to 4X the upper limit of the normal range

>4N - 6 patients had value greater than 4X the upper limit of the normal range

Among the 128 patients, the same patients may have more than one abnormal values post-injection.

Therefore the total number of patients with pre-injection abnormal alkaline phosphatase is very small especially at the higher abnormal values (only 44 patients had $\geq 3X$).

SGPT

The normal range is 10-40 IU/L

There was a total of 12 patients who have value below 10 IU/L

There was a total of 245 patients who had value greater than normal at 2-4 hours, 24 hours, 48 hours or 72 hours.

2N - 115 patients had value greater than 1X but less or equal to 2X the upper limit of the normal range

3N - 27 patients had value greater than 3X but less or equal to 3X the upper limit of the normal range

3N - 11 patients had value greater than 4X but less or equal to 4X the upper limit of the normal range

4N - 9 patients had value greater than 4X the upper limit of the normal range (160 IU/L)

Similarly the same patient may have abnormal values at different time intervals and the total number of patients with abnormal SGPT is very small.

SGOT and Total bilirubin

Similarly, the total number of patients for the above two abnormal factors are small. However, the reviewer did not compose any separate tables

Adverse Events

Adverse events was examined in patients from all phase 2 and US clinical trials who had alkaline phosphatase, SGPT, SGOT and/or bilirubin values above the upper limit of the normal range pre-injection. There was a total of patients 2050. The sponsor presented the following table :

	High Alk. Phos	High SGPT	High SGOT	High Total Bilirubin
Total No. of Pts.	250	185	150	37
N(%)	29(11.6)	20(10.8)	13(8.7)	4(10.8)

Reviewer's comment

It is not known why the sponsor chose the total number of 2050. Previously, in the analysis of liver function test data only 1393 out of 2055 patients was selected.

The sponsor concluded that Magnevist had no effect on liver enzymes, although it may have a transient and reversible effect on total bilirubin. In addition, Magnevist was well tolerated in patients with liver lesions who had normal and/or abnormal liver function test values prior to receiving the drug.

Reviewer's comment

The number of patients with abnormal pre-contrast liver function tests was too small.

(3) ASSESSMENT OF THE PROTEIN BINDING PROPERTIES OF MAGNEVIST INJECTION (page 36)

The sponsor stated that protein binding of Gd-DTPA was investigated at 0.1 mmol/L concentrations of gadolinium (Gd-DTPA)

using in vitro equilibrium dialysis and ultrafiltration methods. The results indicate that protein binding of Gd-DTPA is essentially zero (0) percent.

Reviewer's comment

This section must be reviewed by FDA Pharmacokinetics Division.

(4) DETERMINATION OF COMPARTMENT PHARMACOKINETIC PROFILES OF MAGNEVIST IN TARGETED IMAGE TISSUE COMPARTMENTS. (page 37)

The sponsor agreed to perform a time/intensity curve using a single transaxial section at the level of the liver including representative tissues from the liver, kidneys and skeletal muscle. The image-intensity curve will serve as a surrogate for the pharmacodynamics of gadolinium at the target tissue sites.

Reviewer's comment

The sponsor's proposal appears reasonable. Comments will be provided upon the receipt of the protocol.

ATTACHMENT 1

The sponsor submitted 6 literature references.

- (1) Lackner Krache Th, Gots R, Haustein J: The Dialysability of Gd-DTPA. IN: Byder G, et al, ed. Contrast Media in MRI (International Workshop Berlin, February 1-3, 1990) Brinklann 36, The Netherlands:Medicom Europe; 1990:321-326.

10 patients with renal failure requiring dialysis after the administration of Gd-DTPA 0.1 mmol/kg. 70% of the initial concentration was eliminated from the plasma during each 3 hour dialysis period. About 97% of the initial concentration was eliminated from the body after three hemodialyses in 3 consecutive days. After the third dialysis there was less than 5% of the initial concentration of Gd-DTPA demonstrable in plasma. Fecal specimens collected from the time period of the first 24 hours after i.v. contrast administration, less than 0.1% of the dose of contrast agent was recovered from these fecal specimens. No contraindication exists for the use of Gd-DTPA in patients with renal failure requiring dialysis.

- (2) Haustein J, Schuhmann-Giampieri G: Elimination of Gd-DTPA by means of hemodialysis. Eur J Radiol 1990; 11:227-229.

The author described a 24 year old male with end stage renal failure who received 0.1 mmol/kg for MRI. After five consecutive hemodialyses within 6 days, only 1.5% of the administered dose remained in the body (or 98.5% elimination).

- (3) Choyke PL, Frank JA, Webb D. Filling-Katz MR: Case Report: Gadopentetate Dimeglumine Enhanced MRI in an Anephric Patient on Dialysis. Clin Radiol 1990; 41:430-432.

The author described a 28-year-old male anephric patient who received 0.1 mmol/kg Gd-DTPA for MRI. Dialysis was performed within 16 hour of the injection and lasted 4 hour. Pre- and post-dialysis BUN were 74 mg/dl and 39 mg/dl respectively. Serum gadolinium determinations were obtained immediately prior to injection, immediately after injection, at the inset of dialysis (arterial side and venous side separately) and after dialysis. The results (in parts per million) were <1, 303, 30, 23, 22 respectively. Parts per million is roughly equivalent to micrograms per millimeter. The initial Gd level of 303 p.p.m. was reduced 10 fold to 30 p.p.m. within the 16 hours prior to dialysis due to entry of Gd-DTPA into the extracellular fluid. The relatively poor extraction efficiency (venous concentration of 23 p.p.m. early and 22 p.p.m. late in dialysis) indicates a re-establishment of equilibrium between intravascular and extracellular spaces. The author concluded that one standard dialysis session is insufficient to clear a standard dose of Gd-DTPA.

- (4) Choyke PL, Girton ME, Vaughan EM, Frank JA, Austin HA: Clearance of Gadolinium Chelates by Hemodialysis: An in vitro Study. In press - JMRI.

Each of three agents, Gd-DTPA (Magnevist), Gd-DO3A (ProHance) and Gd-DTPA-BMA (Omniscan) were diluted in plasma and saline and were dialyzed in a standard clinical manner at rates of 0-300 cc/min. Urea and creatinine clearance rates were also determined. The clearances were (clearance in cc/min with 95% confidence interval):

Gd-DTPA 74	Gd-/dO3A 67	Gd-DTPA-BMA 67
, urea 180	and creatinine 142	

Assuming that each contrast agent is distributed in a theoretical reservoir equivalent to the volume of extracellular water, the hypothetical dialysis times for complete removal of the agent range at plasma flow rates of 300 cc/min. Consequently, the use on gadolinium based contrast agents does not appear to require a substantial modification of maintenance dialysis schedules.

- (5) Rowland M and Tozer T. Clinical Pharmacokinetics: Concepts and Applications 2nd edition, Philadelphia, PA; Lea & Fabiger; 1989, 222-237

Based on the above chapter of the book, the sponsor believed that Pediatric trial was not necessary. However, based on the clinical experience and Martin's data (RSNA), the renal clearance of drug are different. (see reviewer's comment in this review, pages 4 and 5)

- (6) Schuhmann-Giampieri G, Clauss W, Drestin GP:
Pharmacokinetics and safety of Gd-DTPA in patients with
impaired renal function. IN: Byder G, et al. ed. Contrast
Media in Netherlands:Medicom Europe; 1990:313-319.

Depending on the degree of renal insufficiency, the glomerular filtration rate and the creatinine clearance of the patient are decreased which is parallel to the decrease in Gd-DTPA clearance from serum in a linear regression line. Thus the elimination half-life for both creatinine and Gd-DTKPA are increased as follows:

Renal Insufficiency	Creatinine clearance	Elimination T1/2 for Gd-DTPA
Slight		
Moderate		4 hr
Severe		10 hr

Although elimination of Gd-DTPA was prolonged, recovery of Gd-DTPA in urine was complete. Up to 100% of the dose administered was recovered in urine 2 days after injection (similar to patients with normal renal function). Only for patients with very severe renal insufficiency (clearance <20 ml/min) was elimination of Gd-DTPA extremely prolonged (T1/2 up to 30 hours) and recovery of Gd-DTPA in urine within the observation period was less complete ($66.0 \pm 13.3\%$). Therefore in this group of patients, hemodialysis might be considered. Recovery of Gd-DTPA in feces was less than 0.3% of the dose administered, indicating very little extrarenal elimination even in patients with strongly impaired renal function. Renal functional parameters (creatinine, urea and creatinine clearance) did not change after administration of Gd-DTPA and no nephrotoxic effects were observed; nor were the functional parameters of the liver changed.

ATTACHMENT 2

Assess the protein binding properties of Magnevist injection

Reviewer's comment

This section should be reviewed by FDA biokinetics section

Reviewer's recommendation

- (1) Data indicate that fewer adverse events were observed in smaller, younger or female patients. If this observation is true, patient surface area vs dose should never be considered in this class of agents. (see attached Biostatistics review)

There is a conflict in pediatric GFR data between Rowland and Aperia. The sponsor should provide a final resolution. Since this group of patients (especially extremely young) are difficult to recruit, the pediatric studies must be separated from the main trial.

(2) Renal impairment -

Reports 9026 and 8974 (see attached) are insufficient to support drug labeling change.

Report 92106 was incomplete (see attached)

Haptic impairment -

The number of patients with moderate to severe liver function is very small. This section should be reviewed by FDA biostatistics Division.

(3) Data on protein binding are acceptable. This section must be reviewed by FDA Pharmacokinetics Division

(4) The proposed trial outline for targeted image tissue is acceptable. A formal submission is necessary to derive any conclusion.

/S/

H. W. Ju, M.D.

6/12/95

Group leader's comments:

With the exception of patients with impaired renal or hepatic function and the very young, I see no safety problems. We need more data in subjects with hepato/renal disease. Await STATS + Pharmacokinetics input
A-E Jones 6/24/95

BEST POSSIBLE COPY

A. E. Jones, M.D.

Orig. NDA 19-596, S-009
HFD-160/MO/H.Ju
HFD-160/CSO/R.Blav
HFD-160/CHE/M.Salazar
HFD-160/PHA/J.Melograna
HFD-160/Init. by A.E.Jones

IBM:MAGNV-NS-009

no stats
/S/ 6/24/95
(await additional review)

Division of Medical Imaging, Surgical
and Dental Drug Products

AUG 26 1993

NDA #19-596/S09

Medical Officer Review

Sponsor:

Date Competed: July 7, 1993

Berlex Laboratories
300 Fairfield Road
Wayne, NJ 07470-7358

Re: Acting Division Director's Comments completed Dec. 12, 1992, on Medical Officer's Review completed August 13, 1992, of Magnevist Injection NDA 19-596/S09.

1. Dr. H. W. Ju completed a review of Magnevist Injection on Aug. 13, 1992, that was commented on by Acting Division Director Dr. Wiley Chambers. Dr. Chambers's conclusions were that "The studies as submitted do not provide sufficient information to support the safety and efficacy of Magnevist to facilitate visualization of extracranial head and neck lesions ..." Dr. Chambers raised a number of questions that were forwarded to the company and these questions were answered in a letter dated June 29, 1993.

The questions raised by Dr. Chambers will be listed with his comments and this will be followed by the answers supplied by the sponsor. A statement for resolution of Dr. Chamber's criticisms in light of the sponsor's reply is suggested after the company response.

Study 202-17

- (1) Based on the MOR, the area of involvement was identified as the oral cavity, pharynx, maxillary sinus, larynx and other miscellaneous locations.

Comments: It is not clear what areas are included in "other miscellaneous locations." Approval for extracranial head and neck should include evaluations of the ocular and auditory systems in multiple studies.

Sponsor Response:

The eleven "other" areas of involvement are:

Pleomorphic adenoma of soft palate
Right side vascular tumor - neurilemoma
Acinic cell carcinoma of parotid
Carotid body tumor of left neck
Pleomorphic adenoma of right submandibular area

Hemangiopericytoma of parotid
Spindle cell carcinoma of left face
Squamous cell carcinoma of left neck
Glomus vagale of right neck
Large cell lymphoma of throat
Hodgkin's lymphoma of left neck

Resolution:

In the claim for visualization of head and neck tumors by Berlex, I would suggest they add a sentence or two saying that insufficient evidence was provided to include the ocular and auditory systems in the claim.

- (2) The MOR identifies the methods used to make the referral diagnosis.

Comments: Only 14 of 27 patients have been accounted for. The MOR states that staging was not done on all patients, but does not include the reason. If "clinical symptoms" is included as a possible means of staging, all patients should have been included. The inclusion of patients with previous MRIs is questionable. Did these patients also have a previous MRI contrast agent?

Sponsor Response:

Referral staging was done for only those patients who had squamous cell carcinoma, and there were only 9 such patients out of the total 27 patients. Investigators were not asked to indicate in the CRF if the MRI was with contrast medium. Berlex believed that since Magnevist Injection was not yet approved, that these patients (who had MRI for staging their disease) had MRI with no contrast medium.

Resolution:

The CRF did not include a place for whether or not a previous MRI was with contrast. Because Magnevist was not yet approved it is logical to assume that patients did not have a previous MRI with Magnevist.

- (3) It is reported that additional information about the primary and/or secondary tumors with regard to;

Location	21	scans
Location size	18	"
Location configuration	22	"
Difference in edema	4	"
Difference in necrosis	3	"
Nodal disease	4	"
Number of lesions	1	"

was made comparing the Pre and Post contrast agent scans.

Comments: The method of verification is not stated. Was the new information obtained accurate? It seems unusual that the location of the tumors would change in 21 of 27 scans. Were any of the differences in location, size, or configuration clinically significant? Did the new information lead to any changes in staging or treatment? There is no information concerning the methods used to minimize bias in the reporting of these results.

Sponsor Response:

The investigators were not asked if the additional radiologic information was clinically significant, or if it changed the staging or treatment. The protocol did not require any further verification for their answers.

The investigators were asked several questions in order to compare tumor-node-metastases (TNM) categories pre- and post-injection. However, after the study was completed, it was discovered that only squamous cell carcinomas could be staged.

For those 9 patients who had their disease staged, there were no changes in the staging post-contrast enhanced MRI.

At the time that Protocol 202-17 was written (February 1987), there was no specific statement regarding methods used to minimize bias. However, such a section was added to the latter Protocol 202-30.

Resolution:

Nine patients who were successfully staged before the MRI procedure. The fact that no changes were made in staging after contrast MRI is not interpreted in the clinical setting as a failure in

diagnosis. It is important to know that a staging diagnosis has not changed.

- (4) In the MOR safety evaluations, pt #2001 is reported as: "diplopia at baseline and at the post-injection examination, his right eye was described as being swollen shut and slightly displaced, post-biopsy; there was no papilledema. The change was not considered due to the study drug."

Comments: The clinical description is not logically connected. ...was a biopsy performed between the time of the baseline examination and the injection of contrast? Was it performed between the contrast and non-contrast MRIs? Why wasn't the biopsy information used to correlate the findings on the MRI?

Sponsor Response:

Patient #2001 had a biopsy post-MRI. The CRF for this patient states, "OD: swollen shut post-bx, without papilledema, slightly displaced." The investigator classified this change as not study drug related. The Sponsor did not receive a copy of the biopsy report.

Resolution:

Apparently the patient had aⁿ MRI followed by a biopsy of the eye.

- (5) Two ADR's are listed. Patient #2001 is listed as having a mild injection site burning and patient #20016 is listed as having dizziness for approximately 30 minutes.

Comments: Why wasn't the patient who withdrew from the study after a "small amount of contrast extravasation" included as an adverse reaction? Were there any other patients withdrawn from the study?

Sponsor Response:

Patient 1003 was the only patient who withdrew from the study. --- The Investigator did not consider this to be an adverse experience, and the patient did not have any complaints.

Resolution:

Extravasation of injected test material is generally not thought to represent an adverse reaction of the test drug

Study 202-30

- (1) Based on the MOR, the area of involvement was identified as the oral cavity, tonsil, parotid gland,etc.

Comments: The distribution of cases appears adequate, however, the number of cases in each area should be identified.

Sponsor Response:

<u>Areas of Involvement</u>	<u>Number of Pts</u>
Oral cavity	9
Tonsil	7
Parotid gland	4
Masticator space	1
Lacrimal gland	1
Orbit	4
Neck	10
Sinuses	6
Larynx	3
Laryngopharynx	1
Pharynx	1
Nasopharynx	3
Hypopharynx	1
Posterior pharyngeal area	1
Peripharyngeal area	1
Epiglottis	2
Subglottic trachea	1
Supraglottic area	2
External auditory canal	2

Resolution:

The sponsor has identified the number of cases in each of the areas listed.

- (2) The MOR identifies the methods used to make the referral diagnosis as:

CT	6	patients
CT with contrast	17	"
MRI	2	"
Clinical	41	"
Other (biopsy)	28	"

Comments: The MOR states that more than one method of diagnosis for one patient could be used. These study results should be used to validate the results of the MRI scans. The inclusion of patients with previous MRIs is questionable. Did these patients also have a previous MRI contrast agent?

There is no information concerning the methods used to minimize bias in the reporting of these results. The reported percentages in the MOR are potentially misleading because the denominator is not the total number of patients in the study.

The results are not consistent between studies and not consistent with the blinded readers. The positive rates for additional information are different in this study than the previous study.

Sponsor Response:

For the two patients who had MRI each had clinical examination as an additional method for diagnosis. One patient also had pathology data.

The Investigators were not asked to indicate in the CRF if the MRI was with contrast medium. Since Magnevist Injection was not approved for the evaluation of head and neck lesions, Berlex believes that these patients had MRI with no contrast medium.

Resolution: [See (3)]

- (3) It is reported that additional information about the primary and/or secondary tumors ... was made comparing the pre and post contrast agent scans.

Comments: The method of verification is not stated. Was the new information obtained accurate. It seems unusual that the location of the tumors would change in 24/60 scans. Were any of the differences in location, size or configuration

clinically significant? Did the new information lead to any changes in staging or treatment?

There is no information concerning the methods used to minimize bias in the reporting of these results.

The reported percents in the MOR are potentially misleading because the denominator is not the total number of patients in the study.

The results are not consistent between studies and not consistent with the blinded readers. The positive rates for additional information are different in this study than the previous study.

Sponsor Response:

The Investigators were not asked if the additional radiologic information was clinically significant, or if it changed the staging or treatment.

The Investigators were asked whether the post-gadopentetate dimeglumine MRI impression differed from the pre-gadopentetate dimeglumine MRI impression.

For 22/60 patients, the Investigators indicated that the post-injection impression differed from the pre-injection impression. All 22 of these patients had additional radiologic information regarding at least 1 parameter.

Fourteen of the 22 patients had additional radiologic information regarding lesion location.

The protocol did not require that the data regarding additional information be directly verified. However, of the 38 patients with additional radiologic information, 26 patients had pathology data post-MRI study. In addition, 6 other patients had pathology data post-MRI. For these 6 patients, however, the Investigators indicated that there was no additional radiologic information post-contrast MRI.

Section H of Protocol 202-30 outlines the "Methods Used to Minimize Bias."

The percentages regarding additional radiological information are based on a denominator of 38 (the number of patients for whom the question regarding

additional radiologic information was answered "yes") and not on the total patient population of 60. This is noted in footnote number 4 on the bottom of the reference page. (Vol 5, Pa 8)

Additional radiologic information was not a key variable for this indication, or for any of our approved indications, i.e., brain, spine and pediatric. The 2 key variables, used to test the difference between Investigators and between studies, were the Global Evaluation: Post-contrast enhancement of a lesion and contrast scores.

The difference between studies for the percentage of patients with "Yes" responses for the contrast enhancement question was not significantly different ($p=0.72$).

There was a significant difference between the Contrast Score difference ($p=0.0047$), but the difference was in magnitude, not in direction.

Resolution:

Previous MRI studies could not be done with contrast since no approved contrast material was available.

"Methods Used to Minimize Bias" was included in protocol 202-30.

The CRF did not require the Investigator to give an opinion as to whether or not the contrast MRI changed the staging or treatment of the patient, i.e., whether or not management of the patient was changed. The study was designed to determine whether or not the reading of the MRI by the Investigator after contrast differed from the reading without contrast.

The sponsor states that for 22/60 patients the post contrast reading did differ from the MRI without contrast. Fourteen of these 22 had additional information provided regarding location of the lesions. This finding may not have changed the staging but very likely could change the treatment. The importance of this finding has been explained by Dr. Ju and does not suggest that the MRI reading without contrast was in error but rather had insufficient information that was supplied by the

contrast MRI.

It is not clear to what Dr. Chambers is referring when using the term "positive rate." The sponsor states that there was not a significant difference between the studies for the number of patients for whom a "yes" response was given for the contrast enhancement question. There was a significant difference in the degree of enhancement between the studies, but the difference was in the same direction. This means that all readers agreed that there was increased enhancement but one considered the enhancement stronger than the other.

- (4) Additional Radiologic Information Post-injection was obtained in:

Study 202-17 N = 27
No= 2
Yes=25
95% Confidence Interval = 76-99%

Study 202-30 N = 60
No= 22
Yes=38
95% Confidence Int.= 50-75%

Comments: The results of these two studies are significantly different (i.e., the confidence intervals do not overlap). The studies do not represent reproducibility of the drug product.

Sponsor Response:

Additional radiologic information was not a key variable for this indication, or for any of our approved indications. The 2 key variables, used to test the difference between Investigators and between studies, were the Global Evaluation: Post-contrast enhancement of a lesion and Contrast scores.

The difference between studies for the percentage of patients with "yes" responses for the contrast enhancement question was not significantly different ($p=0.72$). There was a significant difference between the Contrast score difference ($p=0.0047$), but the difference was in magnitude, not in direction.

Resolution:

The sponsor has presented evidence (see above) that additional information relative to either management or staging of patients was made available after contrast was used in the MRI study. This information was not a variable that was designed into the study, therefore, a rigorous statistical treatment cannot be applied to these numbers.

Blinded Reader 91092

- (1) Film sets for a given patient were displayed: pre-injection, followed by post-injection scans. As the pre-gadapentetate dimeglumine injection films were displayed, the Reader completed a written questionnaire for the pre-injection films which was then withdrawn. The films, however, were not then withdrawn. The post-gadapentetate dimeglumine injection films were then displayed and a post-injection film evaluation questionnaire was completed.

Comments: The method used to evaluate the films has a high potential for bias. There is no information concerning the methods used to minimize bias in the reporting of these results.

Sponsor Response:

A meeting was held with the Division on January 28, 1988, to discuss the design of clinical studies intended to support additional indications for Magnevist Injection. The minutes of that meeting, prepared by Mr. Mark Anderson of the division, state that both Drs. Jones and Conca agreed that the random sampling method originally proposed for the blinded reader studies was unnecessary. The minutes reflect a statement made by Dr. Jones as follows: "...it would be more appropriate for the blinded readers to read the films serially, first looking at the pre-contrast scan (so long as the readers were not aware of the investigator's interpretation nor of diagnosis from alternative procedures...".

Resolution:

The reading of the MRI scans was in agreement with the method directed by Drs. Jones and Conca.

- (2) The reader was able to determine the lesion configuration/border in 4/29 (14%) post-dose injection films for which he had not been able to determine the configuration/border in the pre-injection films. He was able to determine the lesion configuration/border in the 1/29 (3%) pre-injection films for which he had not been able to determine the configuration/border in the post-injection films; this difference was not statistically significant ($p=0.17$).

Compared with pre-injection films, the post-injection films showed a change in lesion size in 4/29 films (14%); and a change in lesion location in 3/29 (10%)

Comment: The results in this blinded reader evaluation are considerably lower than those seen in the original study report. This discrepancy in percentages coupled with the lack of statistical significance detracts from the acceptability of the efficacy information.

Sponsor Response:

Although the difference in determination of lesion configuration/border pre-and post-injection was not statistically significant for this blinded reader, it was significant for the other blinded reader. When the 2 blinded reader studies were pooled, the combined results were also significant, with significant difference between the Readers.

The post-injection results are lower than those reported in the originating studies because the questions asked about lesion size and lesion location were different between the Phase 2 and 3 studies, and the blinded reader studies. For the Phase 2 and 3 studies the question was: "Was there additional information about lesion location, lesion size, etc."

For the Blinded Reader studies the question was:
"Compared to the pre-injection images, do the
post-injection images display any change in lesion
size, lesion location?"

Resolution: (See below)

Blinded Reader 91093

- (1) Film sets for a given patient were consecutively displayed: pre-injection, followed by post-injection scans. As the pre-gadapentetate dimeglumine injection films were displayed, the Reader completed a written questionnaire for the pre-injection films which was then withdrawn. The films, however, were not then withdrawn. The post-gadapentetate dimeglumine injection films were then displayed and a post-injection film evaluation questionnaire was completed.

Comments: The method used to evaluate the films has a high potential for bias. There is no information concerning the methods used to minimize bias in the reporting of these results.

Resolution:

The reading of the MRI scans was in agreement with the method directed by Drs. Jones and Conca.

- (2) The reader was able to determine the lesion configuration/border in 11/37 (30%) post-dose injection films for which he had not been able to determine the configuration/border in the pre-injection films. He was able to determine the lesion configuration/border in the 1/37 (3%) pre-injection films for which he had not been able to determine the configuration/border in the post-injection films; this difference was not statistically significant.

Compared with pre-injection films, the post-injection films showed a change in lesion size in 3/37 films (8%); and a change in lesion location in 3/37 (8%)

Comment: The results in this blinded reader evaluation are considerably lower than those seen in the original study report. This discrepancy in percentages

detracts from the acceptability of the efficacy information.

Sponsor Response:

The post-injection results are lower than those reported in the originating studies because the questions asked about lesion size and lesion location were different between the Phase 2 and 3 studies, and the blinded reader studies. For the Phase 2 and 3 studies the question was: "Was there additional information about lesion location, lesion size, etc."

For the Blinded Reader studies the question was: "Compared to the pre-injection images, do the post-injection images display any change in lesion size, lesion location?"

Resolution:

The sponsor suggests that the reason for the discrepancy in percentages is due to different questions being asked. "Additional information" relative to lesion size and location that is asked of an investigator will produce different answers than a question of "any change" of lesion size and location being asked of blind readers.

Conclusion:

The review of this MRI contrast material was done by Dr. Ju using the accepted criteria of previous reviews. Dr. Chamber's rigorous application of statistical analyses do not seem indicated in light of the IND design that was agreed to by the Division.

The criticisms by Dr. Chambers regarding the lack of efficacy data appear to be a matter of quantitation. Since acquisition of these kind of data were not designed into the protocol statistically significant quantitative results cannot be shown by the sponsor. In spite of this deficiency the sponsor is able to show that a *reasonable* number of patients had information provided by the contrast MRI that was important in the diagnosis and management of his disease.

I agree that this NDA be approved as reviewed by Dr. Ju.

/S/

L. M. Lieberman, M.D., Ph.D.
Medical Review Officer

The attached supplement approval letter (Aug 10 1989) for pediatric CNS use in the population of 2-18 years. The same dose is used in head & neck scanning & is equally safe & effective.

/S/

I believe that the sponsor's data supports the use of Magnevist for extracranial (Head & Neck) contrast enhancement.

/S/

Also, As previously noted (8/21/92) this drug has been approved for pediatric use in CNS lesions. The labeling should extend to pediatric use in head and neck as for adults.

/S/

INDICATIONS AND USAGE

MAGNEVIST® Injection is indicated for use with magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormality in the blood-brain barrier. MAGNEVIST® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

—
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—

MAGNEVIST® Injection is also indicated for use with MRI in adults and children (2 years of age and older) to provide contrast enhancement and facilitate visualization of lesions in the spine and associated tissues. There is, however, only limited clinical experience in children for this indication.

CONTRAINDICATIONS

None known.

WARNINGS

8/26/93: Disregard my above comments dated 7/12/93 & 8/24/93. The additional (ADE etc) data needed for ped. claim will only delay the supplemental approval.

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

PHARMACOLOGY REVIEW(S)

APR 14 1995

NDA 19-596

REVIEW AND EVALUATION OF PHARMACOLOGIC AND TOXICOLOGIC DATA

Division of Medical Imaging, Surgical and Dental Drug Products HFD-160

Laraine L. Meyers, Ph.D.
Review Completion: 12 April 1995

DOCUMENT REVIEWED: Re: S-009 (additional comments to revised drug labeling)

SUBMISSION DATE: 10 November 1994

CENTER RECEIPT DATE: 10 November 1994

VIEWER ASSIGNMENT DATE: 15 March 1995

SPONSOR: Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470-7358
(201) 694-4100 FAX (201) 694-9093

PRODUCT: Magnevist

DRUG CATEGORY/INDICATION: Contrast enhancement agent for use with magnetic resonance imaging (MRI)

CHEMISTRY/FORMULATION: Gadopentetate dimeglumine for intravenous injection; see NDA review for details

BACKGROUND: This review provides additional suggestions for select sections of the product labeling, itemized as 25 and 26 in the referenced document. Additions/changes from the sponsor's proposed text are presented as bold text in this review.

25. CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

No long term animal studies have been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

Gadopentetate dimeglumine was not mutagenic either in the Ames test (histidine-dependent *Salmonella typhimurium*) or in a reverse mutation assay using tryptophan-dependent *Escherichia coli*. The drug substance did not cause cellular transformation of mouse embryo fibroblasts, did not induce DNA repair in rat hepatocytes and was not clastogenic in mouse and dog micronucleus assays. A dominant lethal effect on early spermatids was demonstrated in one *in vivo* mouse study after intravenous administration of 6 mmol/kg, but this effect was not observed in a subsequent study.

When administered intraperitoneally to male and female rats daily prior to mating, during mating and during embryonic development for up to 74 days (males) or 35 days (females), **0.1 mmol/kg gadopentetate dimeglumine decreased the number of corpora lutea. Dosing with 2.5 mmol/kg suppressed food consumption and body weight gain (both genders) and decreased the weights of testes and epididymides.**

In a separate study using male rats, 16 daily intravenous injections of 5 mmol/kg gadopentetate dimeglumine caused spermatogenic cell atrophy. This atrophy remained 16 days following the last dose. Atrophy was not observed at 2.5 mmol/kg.

26. PREGNANCY CATEGORY C

Gadopentetate dimeglumine retarded fetal development when given intravenously for 10 consecutive days to pregnant rats at daily doses of **0.25 mmol/kg (2.5 times the human dose based on body weight)** and when given intravenously for 13 consecutive days to pregnant rabbits at daily doses of **0.75 and 1.25 mmol/kg (7.5 and 12.5 times the human dose, respectively, based on body weight), but not at daily doses of 0.25 mmol/kg.** No congenital anomalies were noted in either species.

There are no adequate and well-controlled studies in pregnant women. **MAGNEVIST®** Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

APPEARS THIS WAY
ON ORIGINAL

/S/

4-12-95

✓ Laraine L. Meyers, Ph.D. / Date
Acting Supervisory Pharmacologist

CC: Orig NDA
HFD-160/DivFile
HFD-160/CSO/Blay
HFD-160/MO/Ju
HFD-160/SMO/Jones

/S/

4-14-95

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

STATISTICAL REVIEW(S)

07
MAR 23 1995

STATISTICAL REVIEW AND EVALUATION

NDA #: 19-596, S-009, SE5-009

Applicant: Berlex Laboratories

Drug: Magnevist

Indication: Enhancement of Pathologies

Dates: Document Date: 2-10-95
Review Division In-Date: 2-13-95
Received by SERB: 2-17-95

Medical officer: H. W. Ju, M. D.

This review examines the statistical material provided in the

The review c

Statistical Analysis

Method .

(1)

(2)

(3)

(4)

Summary

(1)

(2)

(3) In summary, this

(A

(B)

/S/

A G Mucci Ph. D.
Mathematical Statistician

Concur : Nancy D. Smith , Ph. D

Concur : Satya D Dubey , Ph. D.

cc:

Orig. NDA # 19-596, S-009, SE5-009

/S/
3/22/95
/S/
3-22-95

HFD- 160 Dr. Love
Dr. Blay
Dr. Ju

HFD- 713 Dr. Dubey [File; DRU 1.3.2 NDA]
Dr. Smith

HFD- 344 Dr. Lisook

Chron.
A.G Mucci/x34594/SERB/WordPerfect/3/16/95

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This Review contains four pages of text and tables

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

MICROBIOLOGY REVIEW(S)

914

**REVIEW FOR HFD-160
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

DEC 12 1995

**Microbiologist's Review # 1 of NDA 19-596/SCS-013
November 30, 1995**

- A. 1. APPLICATION NUMBER: 19-596/SCS-013
- APPLICANT: Berlex Laboratories
300 Fairfield Road
Wayne, NJ 07470-7358
2. PRODUCT NAMES: Magnevist Injection
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 0.5 mol/L, sterile solution in 10 ml, 15 ml, and 20 ml glass vials for intravenous use.
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Indicated for use with MRI to provide contrast enhancement and facilitate visualization of lesions in the spine and associated tissues, body (excluding the heart), and intracranial lesions.
- B. 1. DATE OF INITIAL SUBMISSION: September 29, 1995
2. AMENDMENT: none
3. RELATED DOCUMENTS: NDA 19-596 and Supplement S-006
4. ASSIGNED FOR REVIEW: October 26, 1995
- C. REMARKS: Magnevist Injection, an approved intravenous drug for magnetic resonance imaging, is produced by Berlex Laboratories. Berlex notified FDA that
- 

D. CONCLUSIONS:

The
The submission is recommended for approval for issues concerning
microbiology.
The review chemist should look

**APPEARS THIS WAY
ON ORIGINAL**

/S/

Brenda Uratani, Ph.D.
Review Microbiologist

11/30/95

/S/

12/12/95

cc:

NDA 19-596/SCS-013
HFD-160 / File
HFD-160 / CSO/ Williams
HFD-805 / Uratani
drafted by: Brenda Uratani, 9/30/95
R/D initialed by P.Cooney, 9/30/95

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 19-596, S-009

REVIEWER: David J. Lee, Ph.D.

DRUG: Magnevist® Injection
(brand of gadopentetate dimeglumine), 0.1 mmol/kg

SUBMISSION DATE: 2/13/95

SPONSOR: Berlex, Wayne, NJ.

REVIEW DATE: 12/20/95

TYPE OF SUBMISSION: Supplement # 009

SYNOPSIS

Berlex Laboratories, Inc. has submitted NDA 19-596, Magnevist, Supplement #009 to address the agency's comments. Magnevist Injection is indicated for use with magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormality in the blood-brain barrier and to provide contrast enhancement and facilitate visualization of lesions in the spine associated tissues. It is supplied as 469.01 mg/mL of gadopentetate dimeglumine, and the recommended dosage is 0.2 mL/kg (0.1 mmol/kg), administered intravenously, at a rate not to exceed 10 mL/min. The maximum total dose is 20 mL.

The agency requested the applicant to address the following on September 23, 1994 Drug labeling changes

In response, the applicant submitted Drug Labeling changes to the agency on November 10, 1994. According to the medical officer (H.W. Ju, M.D.), the Medical Imaging Division is preparing to respond to the applicant accordingly. In addition, The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the Drug Labeling changes proposed by the applicant, and finds that the proposed Drug Labeling by the applicant required substantial changes. Therefore, the OCPB has proposed an "alternative format" for the **Pharmacokinetics** Section of the label

It also includes revisions to the **Precautions** section and the **Dosage and Administration** section. This "alternative format" of the label proposed by OCPB, was delivered to Dr. Roy Blay, CSO, on July 11, 1995, to be conveyed to the applicant.

In response, the applicant submitted the current supplement which contains

1.

A.

B.

2.

A.

B.

C.

The applicant is encouraged to submit any findings (the individual data must be included) to the agency for review and discussion.

3.

4.

5.

A.

B.

C.

/S/

12/20/95

**APPEARS THIS WAY
ON ORIGINAL**

David J. Lee, Ph.D.
Pharmacokineticist
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/

12/20/95

Concurrence:

Ruth E. Stevens, Ph.D.
Pharmacokineticist, Group Leader
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC:	HFD-160	NDA
	HFD-160	DIV FILE
	HFD-160	/CSO/JSWILLIAMS (1X)
	HFD-160	/OCPB/RSTEVENS (2x)
	HFD-160	/OCPB/DLEE (1x)
	HFD-860	/OCPB/HMALINOWSKI (1X)
	HFD-870	/OCPB/MLCHEN (1X)
	HFD-880	/OCPB/NFLEISCHER (1X)
	HFD-850	/OCPB/LLESKO
	HFD-850	/OCPB/CHRON., DRUG, REVIEWER (3X)
	HFD-340	/VISWANATHAN (1X)
	HFD-205	FOI

**APPEARS THIS WAY
ON ORIGINAL**

DJL/112295/120695/121395

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

ADMINISTRATIVE DOCUMENTS

DW

EXCLUSIVITY SUMMARY for NDA # 19-596 SUPPL # 009

Trade Name Magnevist Generic Name gadolinium pentetate dimeglum.

Applicant Name Berlex Lab, Inc HFD- 160

Approval Date Feb. 28, 1996

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

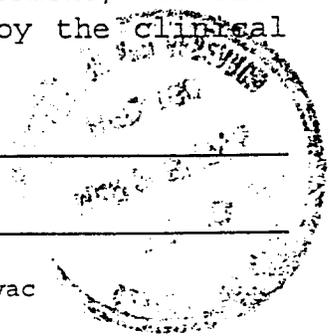
- a) Is it an original NDA?
YES / / NO / /
- b) Is it an effectiveness supplement?
YES / / NO / /
If yes, what type? (SE1, SE2, etc.) SE5

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

HFD-161 / SWilliams



d) Did the applicant request exclusivity?

YES /___/ NO //

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO //

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO //

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-546 _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

**APPEARS THIS WAY
ON ORIGINAL**

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III. PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #. Study # _____

Investigation #__ Study # _____

Investigation # / Study # _____ /

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES / / ! NO / ___ / Explain: _____
! _____
!

Investigation #2 !
IND # YES / / ! NO / ___ / Explain: _____
! _____
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
! _____ !
! _____ !
! _____ !

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
! _____ !
! _____ !
! _____ !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO //

If yes, explain: _____

/S/

3-13-96

Signature

Date

Title:

Consumer Safety Officer

/S/

3/19/96

Signature of Division Director

Date

[Handwritten signature]

cc: Original NDA

Division File

HFD-85 Mary Ann Holovac

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**APPEARS THIS WAY
ON ORIGINAL**

DIVISION DIRECTOR MEMO TO THE FILE

~~19596~~ 19596

NDA: NDA 19-565/ S008 & S009
 DRUG: Magnevist
 SPONSOR: Berlex Laboratories
 INDICATION: 1) Body and 2) Extracranial Head & Neck MRI
 CATEGORY: Efficacy Supplements
 SUBMITTED: November 8, 1991 (S008)
 January 10, 1992 (S009)

Related Reviews: Medical (JU) 12/12/93, 7/6/93, Aug 26, 1993

BACKGROUND: Magnevist was approved for contrast magnetic resonance imaging in the following areas: a) cranial (1998), b) spine (1989) and c) central nervous system (brain and spine) in children 2-17 (1989). On November 8, 1991, supplement 008 was submitted for a Body indication. On January 10, 1992, supplement 009 was submitted for Extracranial Head and Neck imaging in adults and children.

The latter supplements have a tangled regulatory history. In June, 1992, supplement 008 (Body) was considered approvable pending revised labeling. A different revised version from the sponsor, however, was submitted prior to receipt of the division's requests. After a series of interim versions, Dr. Botstein determined that the supplement could be approved (May 16, 1993) and the labeling issues were "resolved" in June, 1993. These revisions included not only suggestions made in June, 1992 but also adjustments to update the format and to develop consistency across the product line. The sponsor was also advised that a new section on Clinical Trials was needed and this section should address all previously approved indications. Because of the amount of sponsor time needed for these revisions and because the sponsor also had one other pending supplement 009, it was felt that supplement 008 for the Body would be approved (effective August 17, 1993). The final labeling for 008 would be addressed with supplement 009. The sponsor was advised (and agreed) that final printed labeling and promotion for 008 should await the combined changes in the package insert.

Subsequent to the approval, the sponsor submitted pre-launch materials which revealed that their definition of "body" was different from ours. In our interpretation body had the same definition as it did for CT scans; i.e, intrathoracic and intra-abdominal. In Berlex's opinion body covered everything they studied. A subsequent meeting was held on October 23, 1993 with Berlex, Drug Advertising and HFD-160. Misleading statements in the advertising were discussed. Of particular concern were the implications of effectiveness in the breast, joints and extremity soft tissues. The sponsor was informed that their data was only supported by a very small sample size. Therefore, these could not be promoted. They were also advised that the final launch material should await the final label revisions.

In January, 1994, Berlex received a copy of a revised package insert with the requested label changes. It specifically included a definition of body as intrathoracic and intra-abdominal. Since then we have not received a response to the draft. The Center for Devices, however, has advised us that Magnevist is being promoted for breast imaging. In light of the above, an approvable pending specific labeling (see attached) letter will be issued. The sponsor should also be advised to stop all promotion of any imaging beyond that which is contained in the draft labeling.

SUPPLEMENT SPECIFICS:

A. Supplement 008: BODY MRI

The two adequate and well controlled trials for the body MRI were derived from a random sample blinded read of two larger open label trials. The original trials had a total of 323 patients. The blinded read provided data on 97 patients. In retrospect, the demographics of the new set are not clear. Anatomical scans were obtained in the following areas: pelvis-23, abdominal cavity 21, retroperitoneal space-13, thorax-11, musculoskeletal (bone, joint and muscle)-22 and Breast-8. The trials compared pre and post Magnevist MRI's for film quality, the determination of the lesion configuration (border, size, location) and number of lesions. The film contrast scores and quality (no contrast, equivocal, good, excellent) were also compared. A confirmation of the diagnosis was not required; but, was available in some patients.

Based upon these data, in additional lesions configuration was identified in 32/97 (33%) of the images and was lost in 4/97 (4%). The lesion size changed in 26/97 (27%), location 9/97 (9%) and other information in 55/97 (57%). The mean number of identified lesions was comparable (pre 1.49, post 1.75) and both increases and decreases were noted. Overall, the following is noted:

Contrast Quality	Pre Magnevist (n=97)	Post Magnevist (n=97)
No Contrast	19	7
Equivocal	23	16
Good	35	33
Excellent	20	41
Mean contrast score	1.58	2.11

Overall contrast differences were also evaluated as follows:

OVERALL RESULTS		
Pre-Magnevist Better Contrast	Equal Contrast Pre and Post	Post-Magnevist Better Contrast
18%	41%	41%

These data therefore indicate that Magnevist provides contrast in a number of areas and lacks or obscures contrast in others. The data were not collected in a manner which could verify which findings are correct. Overall, 9/97 lesions did not enhance. These lesions were 1- hematoma, 1- possible lymphoma, 1- esophageal cancer, 1- liposarcoma, 1-osteoid osteoma, 1- endochondroma, 1 undiagnosed mass, and 1- breast mass. Also, 7/97 lesions seen on pre were not seen on post contrast films. These were 1- endometrial cancer lesion, 1- fatty liver, 1- possible desmoid lesion, 1- liver mass, 1-renal cyst, 1- possible bile duct masses or metastasis, and 1-radiation fibrosis in an unspecified site. Therefore, the package insert should indicate that the MRI enhancement is not a stand alone procedure. Both Magnevist and non-contrast films should be done.

NB: The sponsor indicated that subgroups of patients in the open trial had disease confirmation. Similar information on the blinded read trials were not presented. If Berlex feels that they have additional data to support the broader uses, a new supplement will be needed. This lack of confirmation of findings is more important for some MRI scans than others. For example, if a non-contrast MRI is already approved for imaging an anatomical area (abdomen), then more enhancement alone could be a reasonable goal. If non-contrast MRI in the region is not already approved, then a more rigorous evaluation is needed. Such is the case for breast imaging. Non-contrast MRIs are not indicated for breast masses; the gold standard is mammography. Therefore, a large trial with a least a mammography control and tissue confirmation is needed to support a Magnevist MRI indication.

2) Supplement 009 - Head and Neck MRI

In support of this supplement the sponsor submitted "two" trials which were derived from a split of a phase 2 trial of 27 adults and a phase 3 trial of 60 patients (adults and children). The phase 2 study had 20 men with mean age of 56 and 7 women with a mean age of 46. The phase 3 study had 60 patients with 53 males () and 29 females with a mean age of 53. Of these, an unknown number of patients were between These two trials lacked a blinded read and the trials were of different sizes. Thus, to support the NDA, the sponsor has mixed the subjects based upon study site. The resulting datasets of 35 and 47 patients were blindly read and are refereed to as study A and B.

The blinded reader dataset patient demographics were not submitted. Of the 82 film sets, 66 were evaluated for enhancement. Of these 56/66 were enhanced, 40/66 (67%) the lesion configuration/border was better on post contrast, in 5 (8%) the lesion was better on pre-contrast MRI.

CONTRAST QUALITY	Pre MAGNEVIST	Post MAGNEVIST
No Contrast	5/66	0/66
Equivocal	32/66	16/66
Good	27/66	40/66
Excellent	2/66	10/66
Mean contrast score	1.39	1.91

In general these results are comparable to, but more conservative than, those of the unblinded original studies in which of the global scores indicated that the post-Magnevist scans had more enhancement than the pre-Magnevist scans.

The data was also evaluated for the possibility of more enhancement on the pre-Magnevist scans. Overall the results are as follows:

OVERALL RESULTS		
Pre-Magnevist Better Contrast	Pre & Post Magnevist Equal Contrast	Post Magnevist Better Contrast
9%	44%	55%

The study protocol did not contain a verification step to determine which scans contained accurate findings. Therefore, this suggests that Magnevist contrast MRI should not be used alone.

These trials for head and neck do not meet current standards. Also, because of the recombination of patients, in my opinion, they marginally meet previous standards. These trials are not sufficiently powered to provide meaningful data. Also, the method of trial split and recombination was not planned in advance and as noted in the statistics memorandum, the possibility of bias cannot be excluded. Additionally, the number of pediatric patients is insufficient to support a claim in that population. On the other hand, the data is consistent

with the results in the body supplement. Therefore, given the transition of policy, the head and neck indication can be approved for adults.

The data for children, however, is insufficient. This product is primarily excreted by the kidney. The GFR of children 0-2 and probably of toddlers is different from that of adults. Of note magnevist carries an indication for CNS imaging in children. This was approved in 1989. At the time the approval standards did not require detailed dose adjustment data. The sponsor should perform dose adjustment studies and provide pharmacokinetics data in children for their approved intracranial indication. If they wish to pursue, the extracranial indication, similar information will be needed.

CONCLUSION: As noted above, the action on these supplements has been affect by a dynamic change in division practices. Nevertheless, the two Magnevist supplements present reasonable information to support approval with restrictive labeling. The label should note the limitations of the clinical trials, the lack of verification of findings and the need to compare both pre and post Magnevist MRI images. Information to support labeling in children is insufficient to support approval. Also, in order to clarify existing deficiencies, phase IV commitments are needed and noted below.

ACTION: Approvalbe pending labeling and phase IV commitments

INDICATIONS:

Body (intra-abdominal and intrathoracic (excluding heart))
Extracranial (head and neck)

ADDITIONAL LETTER COMMENTS

1. The use of breast MRI is not contained in the body definition. They cannot promote the use of breast contrast MRI without additional studies which compare the results with mammography, evaluate dose adjustments in relationship to the type of lesions and verify the findings
2. Any future efficacy supplements should be adequately powered to support the trial purpose and should validate the results. The division will be glad to discuss trial controls and outcome measures.
3. Also, a letter on the promotional expectations should also issue from Drug Advertising.
4. The separate and combined demographics of the blinded read datasets should be submitted. These numbers should also be included in the Clinical Trials portion of the package insert.

/S/

Patricia Y. Love, M.D.
Director, Division of Medical Imaging,
Surgical, Dental Drug Products

**APPEARS THIS WAY
ON ORIGINAL**

cc: HFD-160/Div File
HFD-160/Bay
HFD-160/Jones
HFD-160/Ju
HFD-160/Love

9/30/94

Meeting Minutes

Date: 17-Nov-1994
Agent: Magnevist (NDA 19-596)
Sponsor: Berlex
Purpose: Discussion of Breast Indication

FDA Attendees:

Patricia Y. Love, M.D., M.B.A., Division Director
Paula Botstein, M.D., Deputy Director, ODE1
A.E. Jones, M.D. Supervisory Medical Officer
H. Ju, M.D., Reviewing Medical Officer
Joe Pierro, M.D., Medical Officer
Robert Phillips, Ph.D., CDRH
Warren Rumble, DDMAC
Norman Drezin, DDMAC
Roy Blay, Ph.D., CSO

Sponsor Attendees:

June Bray, Director, Drug Regulatory Affairs
Harold Goldstein, M.D., Executive Director, Diagnostic Imaging
Clinical Research and Development
Elise Klein, Corporate Vice President and General Manager
Diagnostic Imaging
Garth McBride, M.D., Vice President Medical and Regulatory Affairs

Points of Discussion:

- The definition of "body" as used by the Division consists of the intra-abdominal and intra-thoracic areas (excluding the heart).
- The sponsor referred to their approvable letter of August 17, 1993, for the whole body, and their meeting with Drug Advertising to discuss draft promotional material.
- An indication for breast imaging would require the submission of supportive data. Any data that the sponsor wished to submit to support a breast indication would be reviewed by the Division.
- The use of specialized imaging coils allows for representation of anatomic morphology and does not address the detection of pathology. Specific claims for an imaging agent would require a greater burden of proof.
- The sponsor was asked to remove references to a breast indication in its labeling and promotion materials. The sponsor indicated its disagreement with this request. The

Division suggested a separation between the indication and the promotion of the agent. The sponsor said that it might have to confer with legal counsel. The sponsor also suggested that a more general indication be developed that would exclude the musculoskeletal system and the breast.

- The sponsor said that it would be in further contact with the Division on these issues.

Minutes by Roy Blay, Ph.D.

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cc: NDA 19-596 Archives
HFD-160/Div. File
HFD-160/Ju/Pierro/Jones
HFD-240/Drezin/Rumble
HFD-160/Blay/Williams

Concurrences: Ju 8-10-95 ; Jones 8-11-95 ; Love 8-25-95 ; Pierro 8-0-95

Meeting Minutes

**APPEARS THIS WAY
ON ORIGINAL**