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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative 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 Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

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.

BEST POSSIBLE COPY

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

BEST POSSIBLE COPY

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.

BEST POSSIBLE COPY

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

BEST POSSIBLE COPY

BEST POSSIBLE COPY

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:

BEST POSSIBLE COPY

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

BEST POSSIBLE COPY

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

BEST POSSIBLE COPY

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.

APPEARS THIS WAY
ON ORIGINAL

/S/

Patricia Y. Love, 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

BEST POSSIBLE COPY

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)

BEST POSSIBLE COPY

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/ 2/17/96
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:H_2O 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 RD 9/22/94
Acknowledgements: Cheever, 9.12.94; Love, 9.13.94
F/T by: CWilson, 9.14.94

SUPPLEMENT APPROVABLE

/S/ 9/22/94

**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 Document Date: Feb 10, 1995
Magnevist (Gd-DTPA)

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.

BEST POSSIBLE COPY

Notes - Agree w/ review completion
/S/ 7/14/95

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

APR 13 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 form 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. 3/7/95

Group leader's comments:

- Regarding question #21: The sponsor's slightly labeling change is unnecessary although reasonably accurate. I agree with Dr Ju's advice to maintain Dr Lovell version as noted in question #21
- In regard to question #9: The sponsor was requested to change the word "urinary" in paragraph 3 under Pharmacokinetics to "renal". That change alone is sufficient.
- Question #25: Studies of Magnevist for "potential effects on fertility" have been conducted according to the sponsor and if these 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 pages 673+674 Vol 21.2 (Annual Report #5) agree - "gadopentetate does not bind to human plasma proteins"
- Question # 26: I agree with the sponsor's recommended labeling

/S/

A. E. Jones, M.D. 3/16/95.

Note: Also need PK to review #9 + 10. Return to me when complete.

/S/ 4/18/95

BEST POSSIBLE COPY

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: MGNVSTS2.LAB

DIV

MAR 24 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)

Phase 4 trials

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

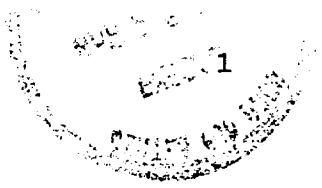
Berlex Laboratories, Inc.
Wayne, NJ 07470-7358

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 mission	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 m2
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 ≥80 mL/min) and 21 had impaired renal function (GRF < 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(±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%) or 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 vale 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)

Similarily 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

Similarily, 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 by 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 ± 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.

/S/ 6/24/95

(await additional review)

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

IBM:MAGNV-NS-009

ADDENDUM TO MEDICAL OFFICER 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 a 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:

Areas of Involvement	Number of Pts
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. Where 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-gadopentetate 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-gadopentetate 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-gadopentetate 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.

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 supplements approval

/S/