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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

STATISTICAL REVIEW(S)

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 (

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 /S/ 3/22/95

Concur : Satya D Dubey , Ph. D. /S/ 3-22-95

cc:

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

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

This Review contains four pages of text and tables

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

MICROBIOLOGY REVIEW(S)

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

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ON ORIGINAL

/S/

11/30/95

Brenda Uratani, Ph.D.
Review Microbiologist

/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

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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

Concurrence:

/S/ 12/20/95

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

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DJL/112295/120695/121395

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019596/S08/S09

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 19-596 SUPPL # 009

Trade Name Magnevist Generic Name gadopentetate dimeglumine

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:

   _____

   _____

Form OGD-011347 Revised 8/7/95; edited 8/8/95

cc: Original NDA Division File HFD-85 Mary Ann Holovac

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 # 19-596 _____

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 /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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 /_X_/

If yes, explain: _____

_____

_____

_____

/S/

Signature Date 3-13-96

Title: Consumer Safety Officer

/S/

Signature of Division Director Date 3/19/96

cc: Original NDA Division File HFD-85 Mary Ann Holovac

DIV

DIVISION DIRECTOR MEMO TO THE FILE

~~APPL~~ 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.

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