

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 21037

APPROVAL LETTER

NDA 19-596/S-018
Magnevist® Injection

NDA 21-037 ✓DFS
Magnevist® Pharmacy Bulk Package

MAR - 10 2000

Berlex Laboratories
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Attention: Ms. June Bray
Vice President
Drug Regulatory Affairs

Dear Ms. Bray:

Please refer to your supplemental new drug application dated June 29, 1998, received June 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Magnevist® Injection.

We also acknowledge receipt of your submissions dated September 11, 1998; October 22, 1998; February 22, 1999; March 4, 1999; September 10 and 29, 1999; October 15, 1999; November 5, 8, and 30, 1999; January 27, 2000; February 11, 2000; March 1, 3, and 9, 2000.

Supplement 18 proposed to clarify labeling language for the safety profile of a 0.3 mmol/kg dose of Magnevist® Injection. NDA 21-037 provides for a new, multiple use Pharmacy Bulk Package of Magnevist® Injection.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the enclosed labeling text, and as agreed upon per fax correspondence dated February 11, 2000; March 3, 2000; and March 9, 2000. The labeling is identical for both NDA's with the exception of language that is unique to a pharmacy bulk package. Accordingly, the supplemental application NDA 19-596/S018 and NDA 21-037 are approved effective on the date of this letter. Also, in accordance with Dr. Lumpkin's letter of January 28, 1999, this constitutes final printed labeling (FPL), which must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels).

Please submit 20 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 "FPL for approved supplement NDA 19-596/S-018." Approval of this submission by FDA is not required before the labeling is used.

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

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

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, call Tia Harper-Velazquez, Pharm.D., Regulatory Project Manager, at (301) 827-7510.

Sincerely,



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

Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21037

APPROVABLE LETTER

Harper

NOV 10 1999

NDA 21-037

DFS
12/3/99

Berlex Laboratories
Attention: Ms. June Bray
Director, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Bray:

Please refer to your new drug application (NDA) dated September 10, 1999, received September 13, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Magnevist® (Pharmacy Bulk Package) (gadopentetate dimeglumine) Injection.

Also, we acknowledge receipt of your submission dated September 2, 1999. However, your submission of September 10, 1999 constituted a complete response to our approvable letter of August 26, 1999.

We have completed the review of this application, and it is approvable as a new multiple use Pharmacy Bulk Package that is not intended for direct infusion. Before this application may be approved, it is still necessary to resolve outstanding labeling issues from NDA 19-596/S-018. We acknowledge your request to approve the Pharmacy Bulk Pack labeling on the basis of the text currently in use; however, as noted in Dr. Lumpkin's letter dated January 28, 1999, labeling is a cumulative process.

Regarding the outstanding labeling from NDA 19-596/S-018, as you are aware, we are currently considering your proposals and information submitted via fax dated November 5, 1999, and the hospital records in your partial response submission dated November 10, 1999. We await additional comments from your consultants, and we will continue to resolve this matter expeditiously. When final labeling for NDA 19-596/S-018 is determined, it will be the basis for the complete Pharmacy Bulk Package labeling.

Also we note that your fax of November 5, 1999, addressed S-018 labeling, not the Pharmacy Bulk Package revisions requested by the FDA in our facsimile dated October 18, 1999. If you agree to the specific changes in the Pharmacy Bulk Package please indicate your acceptance in your response.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment

NDA 21-037

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Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Tia Harper-Velazquez, Pharm.D., Regulatory Project Manager, at (301) 827-7510.

Sincerely,



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

NDA 21-037

AUG 26 1999

Berlex Laboratories, Inc.
Attention: June Bray
Director, Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045

Dear Ms. Bray:

Please refer to your new drug application (NDA 21,037) dated August 27, 1998, received August 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Magnevist (gadolinium dimeglumine) injection.

We have completed the review of this application, and it is approvable as a new multiple use Pharmacy Bulk Package that is not intended for direct infusion. Before this application may be approved however, it will be necessary to resolve outstanding labeling issues from S-018, and to agree to additional labeling as stated in this letter. Regarding the outstanding labeling from S-018, as you are aware, we are currently considering your proposals and information presented during our meeting of May 21, 1999. When final labeling for S-018 is determined, it will be the basis for labeling the Pharmacy Bulk Package. In addition, there are other labeling revisions for the Pharmacy Bulk Package itself. These are listed below for your information.

I. Immediate Container Label and Carton:

- A. Please be advised that the label storage statement "controlled room temperature between 15°C and 30°C" is in conflict with the new U.S.P. definition of controlled room temperature. Future stability studies of ICH conditions would not adequately support a storage statement with the temperature range (15°C - 30°C) in the labeling. However, an appropriate storage statement would be "store at 25°C" with excursions permitted between "15°C - 30°C". Please revise the label storage statement in accordance with these considerations.
- B. The statement "Pharmacy Bulk Package-Not for Direct Infusion" should be placed immediately after the product name "Magnevist Injection" in a boxed format and made prominent by using bold face type, large size font, or contrasting color.
- C. Revise the statement "Discard unused portion at the end of the examination day" to read "Discard unused portion 12 hours after initial puncture."

- D. Provide space on the immediate container label to record the date and time the closure was entered. e.g., Date Entered: _____ Time of Entry: _____

II. Package Insert (Labeling)

- A. As stated in I A. above, the controlled temperature statement should be revised in the package insert.
- B. The declaration "Pharmacy Bulk Package-Not for Direct Infusion" should be in a boxed format, made prominent, and placed beneath the last sentence of the Description section.
- C. Statements b, c, and e in the Dosage and Administration section should be revised to state the following:
- b) The container should not be removed from the aseptic area during the entire 12 hour period of use.
 - c) The contents remaining after initial puncture should be used within 12 hours.
 - e) Any unused contrast media should be discarded 12 hours after initial puncture.
- D. Delete the following phrase from the end of the 1st sentence in the 2nd paragraph in the Drug Handling section:

In addition, we request that you commit to the following:

1. To revise your stability protocol to include Endotoxin testing at release and at expiration dating. This testing will begin at the start of your commercial batches and continue through ongoing stability batches.
2. To revise the list of specifications and analytical methods (section 3.4.2.3) to include Color as one of the tests performed during stability testing as indicated by the stability data and proposed stability testing protocol. This will begin at the start of your commercial batches and continue through ongoing stability batches.

At the time the labeling for S-018 becomes final, please submit updated labeling for the Pharmacy Bulk Package. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

NDA 21-037

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Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact James Moore, R.Ph., M.A., Project Manager, at (301) 827-7510.

Sincerely,

/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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21037

FINAL PRINTED LABELING

NDA 21-037, Magnevist® Injection
March 10, 2000

MAGNEVIST®
(Brand of gadopentetate dimeglumine)
Injection

PHARMACY BULK PACKAGE - NOT FOR DIRECT INFUSION

PHARMACY BULK PACKAGE - NOT FOR DIRECT INFUSION

DESCRIPTION

Magnevist® (brand of gadopentetate dimeglumine) Injection is the N-methylglucamine salt of the gadolinium complex of diethylenetriamine pentaacetic acid and is an 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.

Magnevist® Injection is a 0.5-mol/L solution of 1-deoxy-1-(methylamino)-D-glucitol dihydrogen [N,N-bis[2-[bis(carboxymethyl)amino)ethyl]-glycinato-(5-)]gadolate(2-)(2:1) with a molecular weight of 938, an empirical formula of $C_{28}H_{54}GdN_5O_{20}$, and has the following structural formula:

[Insert the Structure here]

Each mL of Magnevist® Injection contains 469.01 mg gadopentetate dimeglumine, 0.99 mg meglumine, 0.40 mg diethylenetriamine pentaacetic acid and Water for Injection. Magnevist® Injection contains no antimicrobial preservative.

Magnevist® Injection has a pH of 6.5 to 8.0. Pertinent physicochemical data are noted below:

PARAMETER

Osmolality (mOsmol/kg water)	@37 °C	1,960
Viscosity (CP)	@20 °C	4.9
	@37 °C	2.9
Density (g/mL)	@25 °C	1.195
Specific Gravity	@25° C	1.208
Octanol: H ₂ O Coefficient	@ 25°C, pH 7	log P _w = -5.4

Magnevist® Injection has an osmolality 6.9 times that of plasma which has an osmolality of 285 mOsmol/kg/water. Magnevist® Injection is hypertonic under conditions of use.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of intravenously administered gadopentetate dimeglumine in normal subjects conforms to a two compartment open-model with mean distribution and elimination half-lives (reported as mean \pm SD) of about 0.2 ± 0.13 hours and 1.6 ± 0.13 hours, respectively.

Upon injection, the meglumine salt is completely dissociated from the gadopentetate dimeglumine complex. Gadopentetate is exclusively eliminated in the urine with $83 \pm 14\%$ (mean \pm SD) of the dose excreted within 6 hours and $91 \pm 13\%$ (mean \pm SD) by 24 hours, post-injection. There was no detectable biotransformation or decomposition of gadopentetate dimeglumine.

The renal and plasma clearance rates (1.76 ± 0.39 mL/min/kg and 1.94 ± 0.28 mL/min/kg, respectively) of gadopentetate are essentially identical, indicating no alteration in elimination kinetics on passage through the kidneys and the drug is essentially cleared through the kidney. The volume of distribution (266 ± 43 mL/kg) is equal to that of extracellular water and clearance is similar to that of substances which are subject to glomerular filtration.

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

Pharmacodynamics

Gadopentetate dimeglumine is a paramagnetic agent and, as such, it develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by the paramagnetic agent results in a relatively large local magnetic field, which can enhance the relaxation rates of water protons in the vicinity of the paramagnetic agent.

In magnetic resonance imaging (MRI), visualization of normal and pathological brain tissue depends in part on variations in the radio frequency signal intensity that occur with 1) changes in proton density; 2) alteration of the spin-lattice or longitudinal relaxation time (T1); and 3) variation of the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadopentetate dimeglumine decreases the T1 and T2 relaxation time in tissues where it accumulates. At usual doses, the effect is primarily on the T1 relaxation time.

Gadopentetate dimeglumine does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that do not have an abnormal blood-brain barrier, e.g., cysts, mature postoperative scars. However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of gadopentetate dimeglumine in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of Magnevist® Injection in various lesions are not known.

CLINICAL TRIALS

Magnevist® Injection was administered to 1272 patients in open label controlled clinical studies. The mean age patients was 46.4 years (range 2 to 93 years). Of these patients, 55% (700) were male and 45% (572) were female. Of the 1271 patients who received Magnevist® Injection and for whom race was reported, 82.1% (1043) were Caucasian, 9.7% (123) were Black, 5.3% (67) were Hispanic, 2.1% (27) were Oriental/Asian, and 0.9% (11) were other. Of the 1272 patients, 550 patients were evaluated in blinded reader studies. These evaluated the use of contrast enhancement in magnetic resonance imaging of lesions in the head and neck, brain, spine, and associated tissues, and body (excluding the heart). Of the 550 patients, all patients had a reason for an MRI and efficacy assessments were based on pre-and post-Magnevist® Injection film quality, film contrast, lesion configuration (border, size, and location), and the number of lesions. The protocols did not include systematic verification of specific diseases or histopathologic confirmation of findings.

Of the above 550 patients, 97 patients received 0.1 mmol/kg Magnevist® Injection I.V. in two clinical trials of Magnevist® MRI contrast enhancement for body imaging. Of these 68/97 had MRIs of the internal organs/structures of the abdomen or thorax (excluding the heart); 8 had breast images and 22 had images of appendages. The results of MRIs before and after Magnevist® Injection were compared blindly. Overall additional lesions were identified in 22/97 (23%) of the

patients after Magnevist® Injection. The mean number of lesions identified before (1.5/patient) and after Magnevist® Injection (1.8/patient) were similar. Seven (8%) of the lesions seen before Magnevist® Injection were not seen after Magnevist® Injection. Overall, after Magnevist® Injection, 41% of the images had a higher contrast score than before injection; and 18% of the images had a higher contrast score before Magnevist® Injection than after Magnevist® Injection. Magnevist® MRI of the 8 patients with breast images were not systematically compared to the results of mammography, breast biopsy or other modalities. In the 22 patients with appendage images (e.g., muscle, bone, and intraarticular structures), Magnevist® MRI was not systematically evaluated to determine the effects of contrast biodistribution in these different areas.

Of the above 550 patients, 66 patients received Magnevist® 0.1 mmol/kg I.V. in clinical trials of Magnevist® MRI contrast enhancement of lesions in the head and neck. 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® Injection and 40/66 (61%) had better lesion configuration or border delineation after Magnevist. Overall, there was better contrast after Magnevist® Injection in 55% of the images, comparable enhancement in 44 (36%) before and after Magnevist®, and better enhancement in 9% without Magnevist® Injection.

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

In two studies a total of 108 patients were evaluated to compare the dose response effects of 0.1 mmol/kg and 0.3 mmol/kg of Magnevist® Injection in CNS MRI. Both dosing regimens had similar imaging and general safety profiles; however, the 0.3 mmol/kg dose did not provide additional benefit to the final diagnosis (defined as number of lesions, location, and characterization).

INDICATIONS AND USAGE

CENTRAL NERVOUS SYSTEM: Magnevist® Injection is indicated for use with magnetic resonance imaging (MRI) in adults and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine, and associated tissues. Magnevist® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

EXTRA CRANIAL/EXTRA SPINAL TISSUES: Magnevist® is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to facilitate the visualization of lesions with abnormal vascularity in the head and neck.

BODY: Magnevist® Injection is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to facilitate the visualization of lesions with abnormal vascularity in the body (excluding the heart).

CONTRAINDICATIONS

None.

WARNINGS

As with various other intravenous administrations, caution must be used when administering Magnevist® Injection in patients with predisposition to the development of thrombotic syndromes. (See Precautions.)

Deoxygenated sickle erythrocytes have been shown by *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. Magnevist® Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of Magnevist® Injection to exclude the possibility of increased hemolysis.

Hypotension may occur in some patients after injection of Magnevist® Injection. In clinical trials two cases were reported and in addition, there was one case of vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6-1/2 hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of gadopentetate dimeglumine to these events is uncertain, patients should be observed for several hours after drug administration.

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).

PRECAUTIONS (General)

As with various other injectable products, cases of phlebitis and thrombophlebitis have been reported in association with Magnevist® Injection. In most cases, symptoms presented during or shortly after injection, and generally within 24 hours of injection and responded to supportive treatment. However, in very rare cases of patients who may have underlying potential to develop thrombotic syndromes, thrombosis with fasciitis and surgical intervention (e.g. compartment release or amputation) of the dosed limb have been reported. The

relationship of these events to pre-existing disease, concomitant medications, pre-existing vascular fragility, Magnevist® Injection, or the injection procedure was not established. Patency and integrity of the intravenous line should be determined before administration. As with other intravenous injections, appropriate surveillance of the dosing limb for the development of local injection site reactions following administration of Magnevist® Injection is recommended.

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

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

In a patient with a history of grand mal seizure, Magnevist® Injection was reported to induce such a seizure.

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

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.

Animal studies suggest that gadopentetate dimeglumine may alter red cell membrane morphology resulting in a slight degree of extravascular (splenic) hemolysis. In clinical trials 15-30% of the patients "experienced an asymptomatic transient rise in serum iron." Serum bilirubin levels were slightly elevated in approximately 3.4% of patients. Levels generally returned to baseline within 24 to 48 hours. Hematocrit and red blood cell count were unaffected and liver enzymes were not elevated in these patients. While the effects of gadopentetate dimeglumine on serum iron and bilirubin have not been associated with clinical manifestations, the effect of the drug in patients with hepatic disease is not known and caution is therefore advised.

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 judgement 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 disorder, 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.

LABORATORY TEST FINDINGS

Transitory changes in serum iron, bilirubin, and transaminase levels have been reported in patients with normal and abnormal liver function. (see **PRECAUTIONS-General**)

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

Long term animal studies have not been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

A comprehensive battery of *in vitro* and *in vivo* studies in bacterial and mammalian systems suggest that gadopentetate dimeglumine is not mutagenic or clastogenic and does not induce DNA repair in rat hepatocytes or cause cellular transformation of mouse embryo fibroblasts. A dominant lethal effect on early spermatids was demonstrated *in vivo* in the mouse in one study after intravenous administration of 6 mmol/kg but was not verified in a follow up study.

When administered intra peritoneal 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), gadopentetate caused a decrease in the number of corpora lutea at the 0.1 mmol/kg dose level. After daily dosing with 2.5 mmol/kg suppression of food consumption and body weight gain (males and females) and a decrease in the weights of testes and epididymides were also observed.

In a separate experiment in rats, daily intravenous injections of gadopentetate dimeglumine over 16

days caused spermatogenic cell atrophy at a dose level of 5 mmol/kg but not at a dose level of 2.5 mmol/kg. The atrophy was not reversed within a 16-day observation period following the discontinuation of the drug.

PREGNANCY CATEGORY C

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 were not conducted in pregnant women. Magnevist® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

C¹⁴ labeled gadopentetate dimeglumine was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. Less than 0.2% of the total dose was transferred to the neonate via the milk during the 24-hour evaluation period. It is not known to what extent Magnevist® Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Magnevist® Injection is administered to a nursing woman.

PEDIATRIC USE

The use of Magnevist® Injection in imaging the Central Nervous System, Extracranial/Extraspinal tissues, and Body have been established in the pediatric population from the ages of 2 to 16 years on the basis of adequate and well controlled clinical trials in adults and safety studies in this pediatric population. (See Clinical Trials for details).

Safety and efficacy in the pediatric population under the age of 2 years have not been established. Magnevist® Injection is eliminated primarily by the kidney. The pharmacokinetics of Magnevist® Injection in neonates and infants with immature renal function have not been studied.

(See Indications and the Dosage and Administration)

ADVERSE REACTIONS

The mean age of the 1272 patients who received Magnevist® Injection was 46.4 years (range 2 to 93 years). Of these patients, 55% (700) were male and 45% (572) were female. Of the 1271 patients who received Magnevist® Injection and for whom race was reported, 82.1% (1043) were Caucasian, 9.7% (123) were Black, 5.3% (67) were Hispanic, 2.1% (27) were Oriental/Asian, and 0.9% (11) were other. The most common adverse event is headache with an incidence of 4.8%. The majority of headaches are transient and of mild to moderate severity. Nausea is the second most common adverse experience at 2.7%. Injection site coldness/localized coldness is the third most common adverse experience at 2.7%. Dizziness occurred in 1% of the patients.

The following additional adverse events occurred in fewer than 1% of the patients:

Body as a Whole: Injection site symptoms, namely, pain, localized warmth, and burning sensation; substernal chest pain, back pain, fever, weakness, generalized coldness, generalized warmth, localized edema, tiredness, chest tightness, trembling, shivering, tension in extremities, regional lymphangitis, and anaphylactoid reactions (characterized by cardiovascular, respiratory and cutaneous symptoms) rarely resulting in death.

Cardiovascular: Hypotension, hypertension, arrhythmia, tachycardia, migraine, syncope, vasodilation, pallor, nonspecific ECG changes, angina pectoris, death related to myocardial infarction or other undetermined causes, phlebitis, thrombophlebitis, deep vein thrombophlebitis, compartment syndrome requiring surgical intervention.

Digestive: Gastrointestinal distress, stomach pain, teeth pain, increased salivation, abdominal pain, vomiting, constipation, diarrhea.

Nervous System: Agitation, anxiety, thirst, anorexia, nystagmus, drowsiness, diplopia, stupor, convulsions (including grand mal), paresthesia.

Respiratory System: Throat irritation, rhinorrhea, sneezing, dyspnea, wheezing, laryngismus, cough, respiratory complaints.

Skin: Rash, sweating, pruritus, urticaria (hives), facial edema, erythema multiforme, epidermal necrolysis, pustules.

Special Senses: Tinnitus, conjunctivitis, visual field defect, taste abnormality, dry mouth, lacrimation disorder (tearing), eye irritation, eye pain, ear pain.

OVERDOSAGE

Systemic consequences associated with overdose of Magnevist® Injection have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of Magnevist® Injection is 0.2 mL/kg (0.1 mmol/kg), administered intravenously, at a rate not to exceed 10 mL per 15 seconds. Dosing for patients in excess of 286 lbs has not been studied systematically.

DOSE AND DURATION OF MAGNEVIST® INJECTION BY BODY WEIGHT		
Body Weight		Total Volume (mL) *
Pounds	Kilograms	
22	10	2.0
44	20	4.0
66	30	6.0
88	40	8.0
110	50	10.0
132	60	12.0
154	70	14.0
176	80	16.0
198	90	18.0
220	100	20.0
242	110	22
264	120	24
286	130	26
* Rate of Injection: 10 mL/15 seconds		

Drug Handling: To ensure complete injection of the contrast medium, the injection should be followed by a 5 mL normal saline flush. The imaging procedure should be completed within 1 hour of injection of Magnevist® Injection.

As with other gadolinium contrast agents, Magnevist® Injection has not been established for use in magnetic resonance angiography.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present.

Pharmacy Bulk Package Preparation:

NOT FOR DIRECT INFUSION

The 100 mL Pharmacy Bulk Package is used as a multiple dose container with an appropriate transfer device to fill empty sterile syringes.

- a) The transfer of Magnevist® Injection from the Pharmacy Bulk Package must be performed in an aseptic work area such as a laminar flow hood using appropriate aseptic technique.
- b) Once the Pharmacy Bulk Package is punctured, it should not be removed from the aseptic work area during the entire 12 hour period of use.
- c) The contents of the Pharmacy Bulk Package after initial puncture should be used within 12 hours
- d) Any unused Magnevist® Injection must be discarded 12 hours after the initial puncture of the bulk package.

IV tubing and syringes used to administer Magnevist® Injection must be discarded at the conclusion of the radiological examination.

Any unused portion must be discarded in accordance with regulations dealing with the disposal of such materials.

HOW SUPPLIED

Magnevist® Injection is a clear, colorless to slightly yellow solution containing 469.01 mg/mL of gadopentetate dimeglumine in rubber stoppered vials. Magnevist® Injection is supplied in the following size:

100 mL Pharmacy Bulk Package; rubber stoppered, in individual cartons; Boxes of XXX,
NDC 50419-188-XX.

STORAGE

Magnevist® Injection should be stored at controlled room temperature, between 15° - 30°C (59° - 86°F) and protected from light. DO NOT FREEZE. Should freezing occur in the vial, Magnevist® Injection should be brought to room temperature before use. If allowed to stand at room temperature for a minimum of 90 minutes, Magnevist® Injection should return to a clear, colorless to slightly yellow solution. Before use, examine the product to assure that all solids are redissolved and that the container and closure have not been damaged. Should solids persist, discard vial.

Caution: Federal Law Prohibits Dispensing Without Prescription. Rx Only.

This product is covered by U.S. Patent No. 4,957,939. The use of this product is covered by U.S. Patent Nos. 4,647,447 and 4,963,344.

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Manufactured for:
Berlex Laboratories
Wayne, New Jersey 07470

Manufactured in Germany

Filename: LBL.BULK.0300

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21037

CHEMISTRY REVIEW(S)

APR - 6 1999

File

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-037

DATE REVIEWED: 1-DEC-98

REVIEW #: 1

REVIEWER: Milagros Salazar-Driver, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-AUG-98	31-AUG-98	1-SEP-98

NAME & ADDRESS OF APPLICANT:

Berlex Laboratories, Inc.
340 Changebridge Road
Montville, NJ 07450-1000

DRUG PRODUCT NAMEProprietary:

Magnevist Injection, Pharmacy Bulk Pack

Established:

Gadopentetate dimeglumine Injection

Code Name/#:

NDC 50419-188-XX

Chem. Type/Ther. Class:

1 S

PHARMACOL. CATEGORY/INDICATION:

DIAGNOSTIC MRI CONTRAST IMAGING AGENT

DOSAGE FORM:

INJECTABLE, PHARMACY BULK PACK

STRENGTHS:

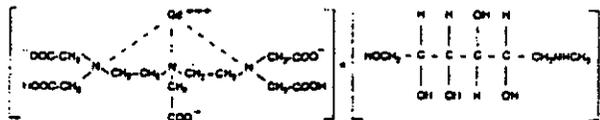
0.5 mol/L

ROUTE OF ADMINISTRATION:

Intravenous

Rx/OTC: Rx OTCSPECIAL PRODUCTS: Yes No (LVP; batch size, 1x = 1805.250 kg)CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-deoxy-1-(methylamino)-D-glucitol dihydrogen[N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-glycinato-5-)]gadolinatate (2-)(2:1)

Empirical formula: C₂₆H₅₆GdN₅O₂₀

MOL.WT: 938

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
NDA	Magnevist Inj.	Berlex Labs., Inc.	Approved	-	2-Jun-88

RELATED DOCUMENTS (if applicable): NDA 19-596 original and supplements S-015, S-006, S-012

CONSULTS: NONEREMARKS:

1. Background: NDA 19-596/SCS-015 was submitted on Mar 24, 1997 for the approval of 5mL and 100mL fill sizes. The company was informed they needed to have a separate NDA for the 100 mL multiple dose vial as a Pharmacy Bulk Package (PBP).
2. Information summary provided in this submission:
 - a. Complete form 356h
 - b. Patent information and Debarment Certification
 - c. CMC information on raw materials, manufacturing procedures, facilities and controls for drug substance and drug product stating to be the same as the currently approved for Magnevist Inj. under NDA 19-596. Only the labeling and usage is to be different. The container closure to be equivalent, only size is different
 - d. Statement on Expiration Dating proposed for this PBP Magnevist Inj. to be identical to the currently approved product, 24 months (with full term stability data). Additional and new statement for multiple dose vial usage of 12 hours after initial puncture (See MICROBIOLOGY REVIEW-- this is not the current usage time after puncture for other parenteral PBP in the market)
3. This product is a LVP, PBP-- multiple dose container. Batch size of _____ kg
4. EER status: overall recommendation: ACCEPTABLE on 2-Nov-98.

CONCLUSIONS & RECOMMENDATIONS:

APPROVABLE pending labeling revisions.

IS/

1-Dec-98

Milagros Salazar-Driver, Ph.D.
Review Chemist, HFD-160/820

IS/

1/13/99

Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-160/820

cc:

Org. NDA 21-037
HFD-160/Division File
HFD-160/Salazar
HFD-160/Leutzinger
HFD-160/Moore
HFD-160/Uratani

filename: N21-037original.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 210037

MICROBIOLOGY REVIEW(S)

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

FEB - 9 1998

Microbiologist's Review #1 of NDA 21-037
February 5, 1998

- A. 1. **APPLICATION NUMBER:** 21-037
- APPLICANT:** Berlix Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, New Jersey 07450-1000
2. **PRODUCT NAMES:** Magnevist Injection (Gadopentetate dimeglumine)
3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 0.5 mol/L,
sterile solution in 100 ml Pharmacy bulk package for intravenous use.
4. **METHOD(S) OF STERILIZATION:**
5. **PHARMACOLOGICAL CATEGORY:** MRI contrast agent
- B. 1. **DATE OF INITIAL SUBMISSION:** August 27, 1998
2. **AMENDMENT:** none
3. **RELATED DOCUMENTS:** NDA 19-596/S-015
4. **ASSIGNED FOR REVIEW:** September 22, 1998
5. **DATE OF CONSULT REQUEST:** September 22, 1998
- C. **REMARKS:**

Magnevist Injection, an approved intravenous drug for magnetic resonance imaging, is produced by Berlix Laboratories. This supplement provides for the addition of the 100 ml pharmacy bulk package. The same contract manufacturer, is employed for the production of the drug product.

D. CONCLUSIONS:

The submission is recommended for approval for issues concerning microbiology.

/S/

2/5/99

Brenda Uratani, Ph.D.
Review Microbiologist

JRC 2/9/99

cc:

NDA 21-037/SCP-016
HFD-160/ Div. File
HFD-805/ Uratani
HFD-160/ Jordan
drafted by: Brenda Uratani, 2/5/99
R/D initialed by P. Cooney, 2/5/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21037

ADMINISTRATIVE DOCUMENTS

SUMMARY MEMORANDUM

NDA: 21-037-
DRUG: Magnevist Injection Pharmacy Bulk Pack
SPONSOR: Berlex
DATE: March 9, 2000

The language contained in the labeling of NDA 21-037, Magnevist Pharmacy Bulk Pack, is consistent to the first approved gadolinium agent, Optimark Pharmacy Bulk Pack, and it is within the current microbiology standards. The resolution of issues for NDA 21-037, were contingent upon the resolution of labeling issues for NDA 19-596/S018. As a result, specific details, including meeting minutes and Tcons for NDA 21-037 can be found in NDA 19-596/S018 for Magnevist Injection.

Submitted by:

/S/

Tia M. Harper-Velazquez, Pharm.D.
Regulatory Project Manager
HFD-160

CC:
Original NDA
HFD-160/Div. File
HFD-160/Harper-Velazquez

Filename: C:/Mycoduments/Magnevist/21037.memo.030900

EXCLUSIVITY SUMMARY FOR NDA # 21-037

SUPPL # _____

Trade Name Magnevist Injection BP Generic Name gadopentetate dimeglumine

Applicant Name Berlex HFD # 160

Approval Date If Known _____

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 question 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.) _____

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:

d) Did the applicant request exclusivity?

YES / / NO / /

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

e) Has pediatric exclusivity been granted for this Active Moiety?

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? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / /

If yes, NDA # 19-596. Drug Name Magnevist Injection

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# _____

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# _____

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.

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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.

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

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

Investigation #1 !
IND # ____ YES / __ / ! NO / __ / Explain: ____
! _____
! _____

Investigation #2 !
IND # ____ YES / __ / ! NO / __ / Explain: ____

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

Investigation #1 !
YES / __ / Explain ____ ! NO / __ / Explain ____
! _____
! _____

Investigation #2 !
YES / __ / Explain ____ ! NO / __ / Explain ____
! _____
! _____
! _____

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

YES /__/

NO /__/

If yes, explain: _____

ISI
Signature _____
Date 03/10/02

Signature of Office/ _____
Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

RECORD OF TELEPHONE CONVERSATION

DATE:
14-Jul-99

Ms. Hartley called to ask questions on a future supplement for NDA 19-596 Magnevist Inj. and to have an update on NDA 21-037 Magnevist Inj. PBP

NDAs:
19-596 &
21-037

She described the intention of the company to create a new tray presentation with all vial sizes and the disposable syringe (recently approved). The tray will make for a new secondary packaging and is intended for distribution to physicians. As a result of the changes in this new secondary packaging, the labels for the product's presentation and PI labeling on presentations will need to be changed.

Initiated by:
Applicant X
FDA

She asked about the need or not for user fees for this supplement. And the turn over time for such supplement.

Made :
by phone X
in person
by Fax

RESPONSE: I told her the review time would be approx. 4 months or less. Regarding the fees, I said it would probably not need to have user fees since it does not seem to have any clinical data or implications.

PRODUCT:
MAGNEVIST INJ.
And PBP

She also stated that the company has not received any information on the review status of NDA 21-037, and almost a year has passed.

FIRM:

RESPONSE: I told her that the CMC was finished last January and I had no information on the letter status. However, I would asked with other disciplines and Project manager to find out its status. I would get back to her on that and the user's fee issue.

Berlex.Labs., Inc

I returned the call with the info. and left a message in her answering machine. RE: the fees, if not clinical data or implications, no fees. supplement-ok. RE: NDA 21-037, I stated that the action letter is linked with the labeling of the original NDA supplement S-018 (Approvable 18-Feb-99) and the labeling safety issues recently discussed in the 21-May-99 meeting. As soon as the labeling issues are resolved the action on NDA 21-037 will be done.

NAME & TITLE:

Jackie Hartley,
Drug Regulatory
Affairs

Phone: (973)
276-2201

cc: orig NDAs
HFD-160 Div. Files
HFD-160 Salazar/
Leutzinger/Moore

Signature:
Milagros Salazar, Ph.D.

IS/

Division:
HFD-160/820

IS/

7/15/99