This single study does not meet the guidelines for supportive literature for an indication due to the following reasons:

a. No safety information was provided
b. Retrospective analysis
c. Inadequate sample size
d. Incomplete methodology details (e.g. post-dose imaging times were not provided for dynamic and delayed scans)
e. Not for market dosing, administration, rate of injection, MR Tesla strength (0.5 and 1.0T versus 1.5T).
f. Formulations used (for MultiHance and the three competitors) were not specified
g. Complete Blinded read protocol were not provided
h. Efficacy analyses were limited and data was pooled for the three comparators

MO Comment: The only trends identified in this article is that MultiHance appears to detect a few more lesions than the pooled comparators (Table #2) and that both MultiHance and the pooled comparators appear to demonstrate improved sensitivity for the paired pre and post-dose compared to the unpaired pre-dose and increased number of detected lesions post-dose compared to pre-dose (Table #3). However, statistical significance cannot be achieved with such small sample size.

Table # 2 Change in Number of Lesions

	MultiHance			Pooled Comparators		
Change in Number of Lesions	0 to 1+	1 to 2+	2 to 3+	0 to 1+	1 to 2+	2 to 3+
Reader #1 (n=66)	3	4	4	1	2	4
Reader #2 (n=56)	3	3	4	0	4	2
	# ↑	# ↓	-	# ↑	# ↓	-
Reader #1 (n=66)	13	0	-	8	3	-
Reader #2 (n=56)	11	1	-	7	1	-

Table # 3 Sensitivity

Sensitivity	MultiHance		Pooled Comparators	
	Pre-dose	Post-dose	Pre-dose	Post-dose
Reader #1 (n=66)	45%	100%	50%	65%
Reader #2 (n=56)	50%	93%	46%	73%

M-5

25 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

II. Summary of Safety Findings

a) Patients with cirrhosis are more likely to report pruritus and injection site reactions.
b) Patients with history of allergy are more likely to report headache, nausea, injection site reactions, vasodilation, paresthesia, taste perversion, dizziness, rash, chest pain, tachycardia, and rhinitis.
c) Please refer to the original NDA clinical review for additional safety concerns.

List of Tables

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/s/

Roger Li
5/23/02 10:21:12 AM
MEDICAL OFFICER

Ramesh Raman
5/23/02 01:38:55 PM
MEDICAL OFFICER
Concur in essence and with the recommendation of Dr. Li. See memo to file. The non-approval recommendation for efficacy (for CNS and safety is justified as discussed in the review and the memo.

Patricia Love
5/24/02 02:31:48 PM
MEDICAL OFFICER
On 5/23/2002, the NDA was administratively split. The CNS indication is approvable;
See my memo to the file for additional comments.

REVIEW CYCLE #1

Submission Date August 20, 2001/
February 26, 2002

Action: Approvable

HFD-160 Clinical Team Leader's Memo to File-Addendum

NDA 21-357 (MULTIHANCE)

Letter Date:	April 27, 2001
Sponsor:	Bracco Diagnostics, Princeton, NJ
Drug Name:	MultiHance (Gadobenate dimeglumine)
Class:	Gadolinium Contrast Agent for MRI
Route:	Intravenous as rapid bolus or infusion
Indication:	For Central Nervous System (including the spine) in Adult
Dose:	CNS Adult- 0.1 mmol/kg

HFD-160 Team:	Medical	Dr. Roger W. Li, MD
	Statistics	Shahla S. Farr, MS
	Chemistry	Dr. David Place, PhD
	Biopharm/Tox	Dr. Tushar Kokate, PhD
	Pharmacology	Dr. Hyun Kim, PhD
	Microbiology	Stephen Langille, PhD
	Project Manager	Thuy Nguyen, MPh

Ramesh Raman, MD
Clinical Team Leader

Concurrence

Patricia Love, MD, MBA
Division Director

This memo is intended to:

1. Acknowledge concurrence with the essence of Dr. Li's primary clinical review and his recommendation.
2. To serve as an addendum to the previous memo to file on the interstitial information submitted by the sponsor.
3. To provide an overview of the main issues of concern in this program (entire database) that justifies the current non-approval recommendation.

The details are provided in the earlier memo to file (to letter dated April 2001) and in the clinical reviews (cycle 1 and cycle 2) of Dr. Li. Following the first review cycle, a non-approval recommendation was made. Before such a formal action was taken, the sponsor (upon notification of such a decision by the Agency and following a meeting with the division) requested the Division to consider "new information" with the hope of aborting a non-approval recommendation.

It is to be noted that even prior to the sponsor's request to review this new information, several additional analyses were performed by the Agency during review cycle one with the hope of identifying relevant and clinically useful information. Further, several of the "new information" that the sponsor submitted were based on suggestions that the Agency provided, again with the hope of exploring the MultiHance database further for improvement in the results. On these grounds, although the sponsor had not identified such potential areas of clinical relevance, the Agency took an active role in steering this program towards identifying the residence of such potentially valuable data.

This new information was submitted over the next several weeks on a constant and regular basis. Dr. Li reviewed all information that was received prior to May 1, 2002. In particular, since the final change on the re-wording of the indication, dose and administration (this third change was for the CNS indication-) was received on May 7, 2002, this information has not been mentioned in Dr. Li's review. However, this did not have an impact on the recommendation. In addition, there were several interim TCONs with the sponsor seeking clarification on the submitted material. This "new information" that was reviewed, essentially consisted of the following:

(a) Literature articles in support of CNS (one article)

(b) One small CNS study that provided only technical information.
(c) Changes (re-wording) in the indication, dose and administration for the made three different times.
(d) Re-analysis of the CNS data for lesions that were zero/one at baseline and > zero/>one post MultiHance (these analyses were independently carried out by the Agency and commented in the previous review.)
(e) Adverse event profile on a subset of patients with cirrhosis without relevant labs.
(f) Adverse event profile for patients with a history of allergy.

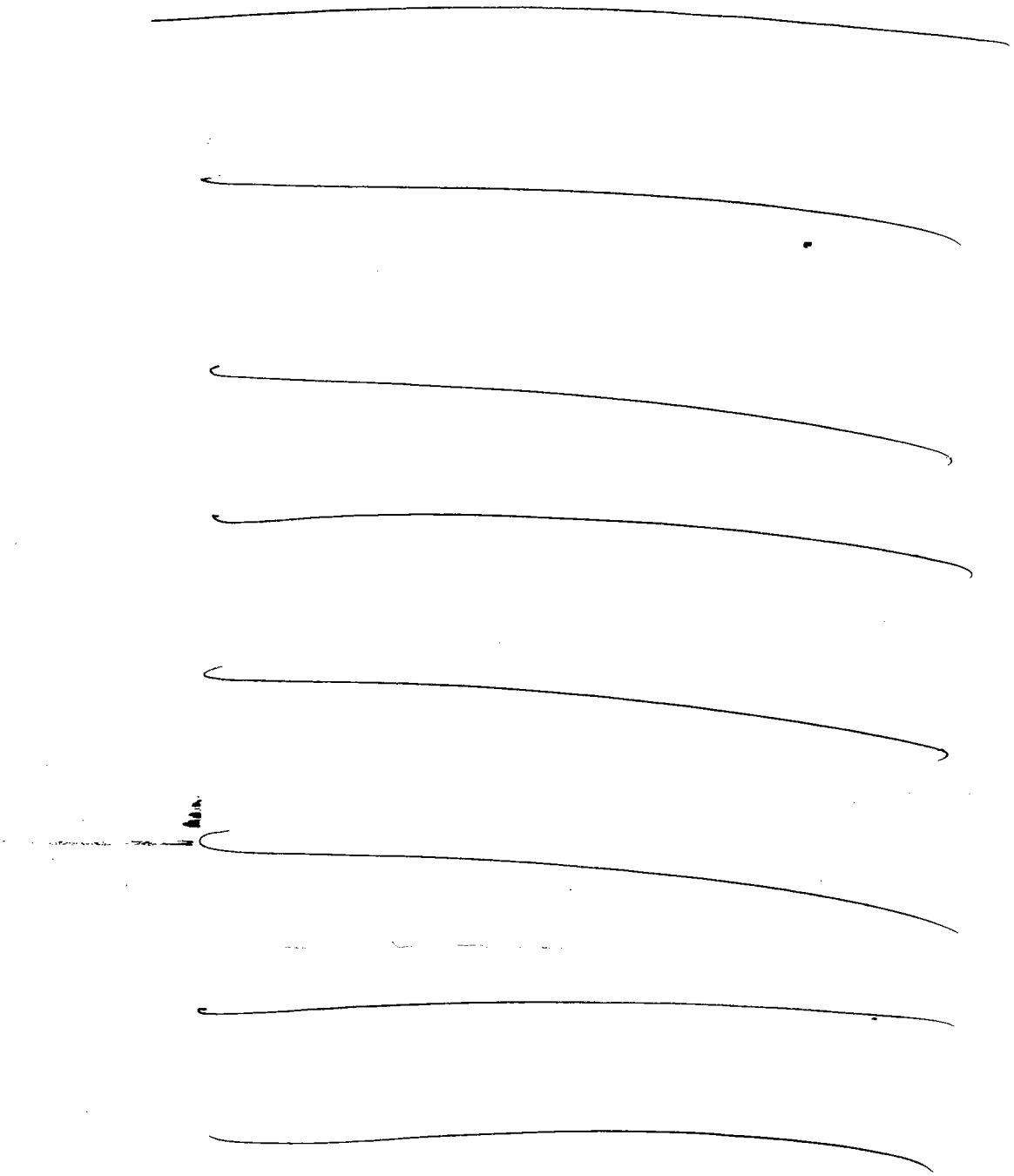
(g) QT data on 11 patients who simultaneously received MultiHance and calcium channel blockers.

Overall, from an efficacy perspective, this new material did not provide clinically useful information that added value to the earlier database to drive an indication. Irrespective [redacted] (and dose and administration), relevant data that could be extracted upon which effectiveness could be determined was limited. As identified in the review cycle 1, the value that one could place on the results from this narrow database was further restricted by the flaws in the study design, the discordance between the sought indications, the doses and the concomitant supportive data, the inconsistencies between the imaging sequences, and several other concerns.

The focus on the new CNS indication was "visualization", which in this program [redacted] The results varied depending on the sequences that were used (lesser sequences in the pre contrast images yielded better results) and, yet were found not be statistically significant. The data did not support the use of contrast (the drug) imaging over non-contrast (the device) imaging. There was no robust data that could be identified for any of the doses and indications (sought or otherwise), and therefore, neither was there justification for the sought dose or doses nor could one identify such data upon which a recommendation for confirmatory studies could be made.

The best results upon which any efficacy assessments could be made were based on the sporadic observations that "something" (with respect to the CNS indication this something refers to detection of lesions by numbers [redacted] ١) was seen after the administration of MultiHance. This "something" was seen with any dose and the value that one could place on the results when one saw "something" (whether lesions by number [redacted]) was further questionable due to the lack its validation with an appropriate standard. When technical data was acquired, such information could not be used in a clinically meaningful way. Specifically, there was failure to connect such information originating from technical primary endpoints [redacted] with clinically relevant endpoints. These technical endpoint assessments did not traverse the required threshold to render the results useful. These inadequacies led to several fundamental questions, why would one give MultiHance (need for contrast- device versus drug)? When would one give MultiHance (indication-clinical setting)? How much should be given (a fundamental question)? When should imaging begin (critical in assessments)? What sequences should be considered (critical in assessments)? The data that would address these questions reside typically in the trials that are conducted during early stages of drug development. In this context, the existing results are very preliminary. Future studies, therefore, as a preliminary step require to identify a dose (least dose for efficacy and safety) and establish that MultiHance MRI does better than non-contrast MRI. Whether this can be achieved is speculative at this time. Any studies to further address efficacy (equivalent to Phase 3 that would drive the indication) would obviously be dependent on the findings from these preliminary studies (trying to establish the dose and that drug is better than device). On these grounds, all the four CNS studies (9A, 9B, 20A and BBG701) provided only "superficial" information and did not extend to the "depths"

that could have positioned MultiHance more favorably. In essence, although it may seem that the database is "large", it really does not carry the necessary weight and provides very little clinically useful information. What needs to be developed in the future is more than what has been developed thus far.



. Of further concern are the unknown effects that MultiHance may have in patients with co-existing hepatic and renal disease (e.g. hepato-renal syndrome).

MultiHance may be handled in this population with underlying metabolic disorders.

These liver safety concerns were discussed with Dr. John Senior (CDER, OPSS), who recommended that approval should not be considered at this time until several of these questions are addressed.

A second safety concern is the effects of MultiHance on the cardiovascular system. The results from the study 43779 (submission of 3-25-02 N-000-BM) involving patients taking calcium channel blockers, in whom the effects of MultiHance on QT interval were measured, did not raise obvious concerns. However, based on the small sample size of eleven patients and the variations in the mechanism of actions between MultiHance and the calcium channel blockers and their relationships to QT interval, these results cannot be generalized and does not address the overall cardiovascular safety concerns of MultiHance as discussed in the earlier memo.

In the equation of risk versus benefit, MultiHance at this time cannot be deemed without risk and the benefits are yet to be identified and validated. There are three other marketed gadolinium agents that currently are available for use and with similar indications. Seeking solace on the grounds that MultiHance is "an other gadolinium agent (based on the familiarity with the concerns of this class) is difficult and not justified because, although MultiHance appears to be made up of the same fabric as the other gadolinium agents in the market, it is the only gadolinium agent that is lipophilic and behaves differently with respect to the liver. Some of the safety concerns occurred following a single dose. Further, the safety concerns can be addressed only with future data/studies and a restrictive label may still be imminent.

In summary, the "new information" did not provide any added clinical value to the previously submitted data that resulted in a non-approval recommendation. The current data is preliminary and has not even identified the dose and has not provided information on whether the drug is better than the device. However, the previously identified liver concerns have only been further amplified. The risks clearly outweigh the hither to unidentified benefits. On these grounds, the previous recommendation of non-approval for efficacy (CNS and safety stands.

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/s/

Ramesh Raman
5/24/02 04:00:33 PM
MEDICAL OFFICER

The non-approval recimmendation is based on the details contained in the two memos to file. Reference is also made to the primary clinical review of Dr. Li. This memo is an addendum to the earlier one.

Patricia Love
5/24/02 05:25:19 PM
MEDICAL OFFICER

In part I agree with the concerns raised by the reviews. See my Addendum to the Division Director's Memo to the File for the final action.

REVIEW CYCLE #1

Submission Date August 20, 2001/ February 26, 2002

Action: Approvable

NDA 21-357 MEDICAL OFFICER'S REVIEW HFD-160

MULTIHANCE

Letter Date:	April 27, 2001
Date Received:	April 30, 2001
Date Assigned:	May 2, 2001
Date Completed:	February 8, 2002 (final version)
Type of Submission:	Industry sponsored NDA
Sponsor:	Bracco Diagnostics P.O. Box 5225 Princeton, NJ 08543
Division:	Medical Imaging and Radiopharmaceutical Drug Products
Medical Officer:	Roger W. Li, MD
Team Leader:	Ramesh Raman, MD
Statistician:	Shahla S. Farr, MS
Chemist:	David Place, PhD
Biopharmacologist:	Tushar Kokate, PhD
Clinical Pharmacologist:	Hyun Kim, PhD
Microbiologist:	Stephen Langille, PhD
CSO:	James Moore
Drug Name:	
Commercial	MultiHance
Generic	Gadobenate dimeglumine
Class of Drug Product:	MRI agent
Proposed:	
"Indications and Usage	*MultiHance is indicated for intravenous use in* [redacted] *magnetic resonance imaging (MRI) of the Central Nervous System* [redacted]
[redacted]	[redacted]
Central Nervous System	[redacted]

MultiHance Dosage and Administration

CNS
Adults
"0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion or bolus injection.

All doses are to "be followed by a saline flush of at least 5 mL.
It is important to ensure that the i.v. needle or cannula is correctly inserted into a vein.
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."
"When MULTIHANCE injection is to be injected using plastic disposable syringes, the contrast should be drawn into the syringe an used immediately."

Imaging

CNS

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation of Approvability

This NDA proposes an adult [redacted] Central Nervous System (CNS) indication [redacted] for MultiHance.

This submission does not contain sufficient information to document how MultiHance enhanced MRI images can improve the [redacted] information to improve the detection [redacted] of lesions with abnormal vascularity and lesions thought to cause an abnormality in the blood brain barrier. Therefore, efficacy is not established.

[redacted] complete safety analyses for QTc interval (and the other ECG parameters), nor a complete adverse event profile and safety parameter subanalyses for all dosed subjects. The frequency of occurence of the common side effects (headache, nausea, injection site reaction, vasodilation, parathesia, taste perversion, and dizziness) are comparable for the existing database to those reported by the other four FDA approved gadolinium MRI agents.

Currently the other gadolinium MRI agents adequately serve the same needs (CNS [redacted]). The sponsor has not supplied sufficient evidence of a clear added efficacy benefit or a comprehensive safety analysis for MultiHance, therefore, the recommendation for this NDA is not approvable.

B. Recommendation on Additional Studies

For [redacted] the CNS [redacted] indications, the sponsor should perform two adequate and well controlled, double blinded, randomized trials with well thought out prospectively defined clinically relevant objective primary endpoints with a clearly described null hypothesis for purposes of appropriate sample size determination. The study should avoid the multiple critical design flaws that were common to several studies detailed in this review.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Programs

MultiHance (gadolinium dimeglumine) belongs to the class of paramagnetic gadolinium MRI contrast agents which when administered intravenously causes enhancement in areas of accumulation.

The sponsor has submitted data and either clinical trial reports or synopses for 4075 subjects, that were administered MultiHance, from 78 completed clinical studies (3960 subjects) and 5 ongoing clinical studies (115 subjects).

The overall safety database (3960 subjects) did not include the subjects from the 5 ongoing studies. About 1/6 of the subjects were from the US, ½ from Europe, and 1/3 from Japan. It also includes 110 US/European pediatric subjects and 743 US/European subjects >65 years of age.

The relevant efficacy database (2757 subjects) consists of 1034 subjects in 21 CNS efficacy studies. The remaining 1203 subjects were divided between studies. The 5 ongoing studies were not included in the efficacy analyses.

B. Efficacy

For the CNS indication, the sponsor proposes that MultiHance can provide ' with unenhanced MRI resulting in improved detection ' of CNS lesions in adults . To this end, the sponsor has evaluated the endpoints of: increase in the level of ' number of lesions.

Out of the 1041 subjects enrolled, only 326 adults and 80 pediatric patients received the proposed single dose of 0.1 mmol/kg dose and 0.5 M formulation. However, none of these adult subjects were in the proposed one supportive or two pivotal key studies. Instead the adult CNS efficacy indication is based upon 210 adult subjects that were given the first 0.1 mmol/kg dose from the 0.1 +0.1 mmol/kg regimen (n=136) or from the

0.1 + 0.1 + 0.1 mmol/kg regimen (n=74).

In spite of the numerous repeated critical design flaws and small relevant sample size, the sponsor has shown that MultiHance is ineffective in improving the evaluation of the mean number of lesions . The proposed CNS indication is not supported and therefore, not approvable.

C. Safety

The total safety database consists of 3960 subjects from 78 studies, which includes 624 US adults (16%), 2013 European adults (51%), 1213 Japanese adults (31%), and 25 US + 85 European pediatric subjects (3%). 55.5% were male and 44.5% were female. 743 of the US/European adults (28%) were greater than 65 years of age (the number of Japanese adults >=65 years old was not provided by the sponsor). The overall racial makeup consisted of: 64% caucasian, 2% black, 1% hispanic, 31% asian, and 1% other or missing.

The sponsor did not include the Japanese subjects (n=1213), pediatric subjects (n=110), and European healthy volunteers (n=63) into the overall analyses reported in the integrated summary of safety or the 4 month safety update. Therefore, the safety reports are based upon the 2574 US and European adults.

When compared to the other four FDA approved gadolinium MRI agents, MultiHance has a similar chemistry (except for viscosity and osmolality), pharmacokinetics, and clinical safety adverse event profile.

Table 1 Chemisty, Pharmacokinetics, and Adverse Event (>0.5%) Comparison

CHEMISTRY					
	MultiHance	Magnevist	ProHance	Omniscan	OptiMARK
Concentration of Active Drug (mg/mL)	529	469	279	287	331
Osmolality (mOsmol/kg @ 37°C)	1970	1960	630	789	1110
Viscosity (MPas@37°C)	5.3	2.9	1.3	1.4	2.0
Density (G/mL @ 20 °C)	1.22	1.20	1.14	1.14	1.16
PH	6.5 to 7.5	6.5 to 8.0	6.5 to 8.0	5.5 to 7.0	5.5 to 7.5
Ionicity	ionic	ionic	nonionic	nonionic	nonionic
PHARMACOKINETICS					
Distribution Half-life (hrs)	0.085 to 0.605	0.200	0.200	0.062	0.222
Elimination Half-life (hrs)	1.2 to 2.0	1.6	1.6	1.3	1.7
Total Body Clearance (mL/hr/kg)	93 to 133	116	90	108	72
Urinary Elimination (by 24 hours)	78 to 96%	91%	94%	95%	NA
ADVERSE EVENTS					
	MultiHance	Magnevist	ProHance	Omniscan	OptiMARK
Headache	2.4	4.8	<1%	<3%	8.4
Nausea	1.8	2.7	1.4	<3%	3.0
Injection Site Reaction	1.6	2.3	<1%	<1%	1.2
Vasodilation	1.2	<1%	-	<1%	2.3
Paresthesia	0.9	<1%	<1%	<1%	2.1
Taste Perversion	0.9	<1%	1.4	<1%	4.4
Dizziness	0.7	1%	-	<3%	3.1

NA = not available

D. Dosing

For the adult [redacted] CNS indication, the sponsor proposes a 0.1 mmol/kg dose of the 0.5 M formulation which may be administered as a rapid intravenous infusion or bolus injection. [redacted]

[redacted]

The sponsor has a very limited efficacy sample size for the proposed CNS ——— indications at the proposed doses and formulation, as discussed in the above Efficacy section II.B.

There is an overall adult and pediatric safety database for the 0.05 mmol/kg dose of 827 subjects (21%) and for the 0.1 mmol/kg dose of 1948 subjects (49%). However, there is a lack of PK data for infants from 6 months to 2 years and the effective databases are limited for certain safety parameters (i.e. QTc intervals immediately post-dose of < 150 subjects).

E. Special Populations

The sponsor has performed 4 pharmacokinetic studies in special populations (n=67). They included a renal impairment study (moderate = 9 and severe =11), a dialysis study (n=11), a hepatic impairment study (n=11), and a pediatric study (n=25).

As expected, for the patients with renal impairment, the elimination half-life is prolonged and the renal clearance and total body clearance decrease as renal function decreases. MultiHance is readily dialyzable, as demonstrated by the mean % of administered dose of gadolinium found in the dialysate fluid being similar to the mean cumulative urinary excretion observed for both the moderate and severely impaired renal patients.

MultiHance is not metabolized in the liver to any significant extent, as evidenced by the pharmaockinetics of hepatically impaired patients being similar to that of healthy volunteers.

The pharmacokinetics in the studied pediatric population (2 to < 16 years of age) is similar to normal adult volunteers. However, the study did not include any infants (< 2 years of age) and only one subject < 5 years of age (3.2 years old) was studied. Therefore, the PK effect resulting from the administration of MultiHance on patients with renal, hepatic, and blood brain barrier immaturity cannot be assessed. The sponsor has studied CNS efficacy on 15 patients under the age of 2, which they admit is too small a number to "draw any reliable conclusion".

The pharmacokinetics of the geriatric population was not studied as an individual special study. The sponsor did not analyze and report the geriatric pharmacokinetic and clinical safety and efficacy results separate from the general adult results. However, without substantiation, the sponsor claims (in the package insert) that "no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly or younger patients". Although the absence of these analyses is not a major cause for recommendation of not approvable, they should be performed and included in the case of resubmission.

Clinical Review

I. Introduction and Background

A. Chemistry and Mode of Action

MultiHance belongs to the class of paramagnetic contrast agents that shortens T1 (longitudinal) and, to a lesser extent, T2 (spin-spin) relaxation times of tissue water protons. These agents distribute (leak) into tissues with abnormal vascularity and alter the tissues' magnetic property and consequently increase image contrast.

MultiHance (gadobenate dimeglumine) is a positive, ionic, paramagnetic gadolinium magnetic resonance imaging agent. It contains a gadolinium ion complexed to a chelating agent. The 0.5M formulation is a sterile, clear, and colorless aqueous hypertonic solution.

Table #2 Identification

Generic Name	gadobenate dimeglumine
Laboratory Code	B19036/7
USAN	gadobenate dimeglumine
CAS No	127000-20-8
Trade Name	MultiHance
Class	paramagnetic gadolinium MRI agent

Selected formulation characteristics are shown in the next table.

Table #3 Chemistry

Density (g/mL)	1.22 at 20°C
Viscosity (mPa.s)	[redacted] 5.3 at 37°C
Osmolality (osmol/kg)	1.97 at 37°C
PH	6.5 to 7.5
Molecular weight	1058
Molecular formula	$C_{36}H_{62}GdN_5O_{21}$

Compared to the other four FDA approved gadolinium MRI agents (Table #1), Multihance has the highest osmolality and viscosity. Magnevist has the next highest osmolality (1.96 osmol/kg) and viscosity [redacted]. Both agents are ionic and linear. The other three agents are nonionic. The ionicity, osmolality, and viscosity are associated with toxicity (See section I. D).

B. Proposed Indication and Dosing Regimen

The sponsor is proposing a CNS indication.

"Multihance is indicated for intravenous use in adults

DOSE	CNS (adults and children)	0.1 mmol/kg (0.2 mL/kg)

C. Regulatory History

1. United States

a. List of major dates: (IND submission, NDA submission, meetings, teleconferences, faxes, and letters)

October 28, 1993	MultiHance was submitted as IND 43,779
November 24, 1993	A teleconference notified the sponsor that a clinical hold was placed on IND 43,779 for both nonclinical and clinical safety concerns. At that time, additional data was requested to support a reasonable margin or degree of safety and toxicity prior to administration to patients in the US.
February 10, 1994	A Divison letter iterated the clinical hold issues, options for removing the clinical hold, and nonclinical hold issues.

March 21, 1994	A teleconference was held with the sponsor on to discuss safety issues and clinical trial design. Submission N008 was received on June 3, 1994 and contained a response to the clinical hold. The responses adequately addressed the major Division concerns.
July 12, 1994	A teleconference removed the clinical hold provided that the sponsor does not proceed
August 30, 1994	A Division letter was sent commenting on the CNS protocol and requested more information. A pre-teleconference meeting was held on April 23, 1997 to discuss the CNS MRI indication.
July 27, 1995	A formal official notification letter telling the sponsor of the removal of the clinical hold was issued.
May 20, 1997	A teleconference was held to discuss the blinded reader protocols for 43,779-9A and 43,779-9B. Objective criteria for image interpretation and independent off-site blinded readers were recommended by the Division.
October 13, 1999	A teleconference was held regarding further ECG recommendations.
July 6, 2000	An End of Phase 2 meeting was held regarding MRA.
April 27, 2001	MultiHance was submitted as NDA 20-357

b. List of clinical submissions and responses to trial design:

N008 received June 6, 1994.
Sponsor's response to clinical hold issues and re-analysis of Phase 2 trial submission N005.

N010 received July 7, 1994.
This consisted of an Phase 2 protocol (021) for CNS MRI. Division comments to this protocol were sent on August 30, 1994.

N012 received August 22, 1994.

A statistical review is dated March 31, 1995. A clinical review is dated October 13, 1994.

N015 dated February 24, 1995.

N019 and/or 020 dated March 1 1996.
This consisted of a Phase 1 protocol amendment for PK in renally impaired patients.

N021 dated April 25, 1996.
This consisted of a Phase 1 PK protocol for renally impaired patients.

Amendment N022 received on April 25, 1996.

N022 received May 16, 1996.

N029 dated November 14, 1996.
The Division draft comments were faxed on November 27, 1996 and stated:

N031 dated November 25, 1996.
This consisted of a Phase 1 protocol for patients requiring hemodialysis.
N033 dated December 12, 1996.
This consisted of two identical Phase2/3 protocols for CNS lesions. Statistical review dated March 12, 1997. Clinical review dated April 18, 1997.
N035 dated January 30, 1997.
This was a response to clinical and statistical comments regarding protocol 43,779-8 (021 a Phase 2 CNS trial). Statistical review dated March 21, 1997
N041 dated April 24, 1997.

N042 received on April 30, 1997.

N050 dated August 22, 1997.
This was a revised statistical analysis in response to previous statistical review of 3/20/97 and teleconference 4/29/97. Statistical review October 7, 1997.
N055 dated November 24, 1997.
This consisted of nonclinical data from prior studies and was reviewed by PharmTox dated January 21, 1998.
N056 was dated December 16, 1997.
This consisted of a Phase 1 protocol evaluation in healthy children. Biopharm review dated March 27, 1998. Clinical review dated February 23, 1998.
N058 dated June 19, 1998.

N068 dated May 14, 1999.
This was a NDA meeting package with a review from PharmTox dated September 21, 1999.

c. Chronological history of contact between the FDA and the sponsor regarding the CNS efficacy indication:

November 24, 1993	A teleconference notifying the sponsor of a clinical hold.
February 10, 1994	A letter to the sponsor (addressed the issues for the clinical hold placed upon the new IND submission on Novermber 24, 1993. The main

clinical efficacy issues concerned the lack of a blinded reader and the lack of an active comparator.

Clinical Hold issues included:
Electrocardiograms should be performed immediately after contrast administration and 8 hours after the last contrast dosing.
Images should be independently reviewed by two blinded radiologists/neuroradiologists who evaluate and compare all pre- and post-contrast images separately and in matched pairs.
Efficacy criteria should also include the [redacted], number of lesions seen or obscured, border delineation, [redacted] of [redacted]
The primary investigator's evaluation may be used as an ancillary confirmatory method of analysis only.
Results should be correlated with an accepted standard to address sensitivity, specificity, and clinical utililty.

[redacted] Image timing should be presented in a blinded manner, e.g. the timing of the pre and post contrast scans should not be recorded on the blinded investigator's copies.
Modify the protocol to include a comparison to an approved gadolinium compound. The sample size should be adjusted accordingly.

Non-hold clinical issues included:
Be prepared to submit the MR images in a digital format.

March 13, 1997 — A fax was sent by the statistician regarding FDA draft comments on the CNS protocol. See sponsor's responses below for more details.

April 29, 1997 — A teleconference was held to discuss CNS protocols 43,779-9A and 9B.

The following information was obtained from the BDI minutes:The sponsor submitteed responses on August 21, 1997 (IND 43,779 N050) to the fax of March 13, 1997, sponsor's version of the minutes to the meeting of April 29, 1997, and a copy of a crossout revision 1 of the statistical analysis plan (dated July 23, 1997).
The following are the important issues addressed in this submission:
BDI agreed to reconsider the 'composite score' approach based on FDA suggestions in choosing one or two representative endpoints. [the sponsor originally used a composite score for [redacted] categories]
BDI agreed to consider the 'non-comparative' scale approach, based on the appropriate selection of endpoints.

[redacted]

No consensus was reached on the use of a truth panel.

August 27, 1997	Submission IND 43,779 N051 was the sponsor's version of the teleconference of May 20, 1997 regarding blinded reader selection. The FDA was concerned with the sponsor's request to use investigators from one study as readers for the other identical study. The FDA discussed the potential bias involved and recommended independent readers be used. The FDA also mentioned that a placebo arm, if added to the study, would indicate the capability of the comparator to show superiority to baseline.
November 14, 1997	Submission IND 43,779 N054 was the sponsor's revision to 43,779-9A and 43,779-9B with Amendment 3. This included the final versions for the statistical plan, off-site imaging evaluation methodology and CRF, and changed the evaluator of the comparative procedure.
June 17, 1999	In house pre-NDA meeting.

[redacted]

FDA inquired about the method used by blinded readers to examine and evaluate images and cautioned the sponsor to insure that blinded readers remain independent so that bias is not introduced into the evaluation of the images. Safety data should be by dose: 0.1 mmol, < 0.1 mmol, > 0.1 mmol

July 16, 1999 — Submission IND 43,779 N069 provided a package that discusses the sponsor's rationale/plan for the pooling of data in the ISS; an updated, more detailed electronic submission plan; and a request to reach closure on the sponsor's proposal to submit synopses for the 40 clinical studies considered to be supportive, with full information to be provided on the clinical pharmacology/pharmacokinetic and eight key studies. The sponsor wanted to arrange multiple T-cons to discuss this package.

July 16, 1999 — Submission IND 43,779 N070 included the sponsor's version of the meeting minutes for pre-NDA meeting on June 17, 1999.

The FDA asked for clarification of the methodology for the off-site reads for CNS Studies 43,779-9A and B19036/020. The FDA requested that any material used for training the off-site readers be included in the NDA. The FDA also requested that the field strengths of the MRI scanners, in addition to the imaging parameters used for each study be included in the NDA. The FDA inquired if the shift tables showing changes in the increase in level of [redacted] for studies 43,779-9A and 9B would be included in the NDA. The FDA reiterated their request for analyses of the primary endpoint by subgroups of age, gender, and race. [redacted]

[redacted] The sponsor and FDA agreed inclusion of this study in the NDA would be appropriate. Other issues discussed concerned liver studies, overall safety, electronic submission, pharmacology/toxicology, CMC, and human pharmacokinetics.

October 13, 1999 — A teleconference was held. This was a follow-up to the pre-NDA meeting of June 17, 1999.

The following information was obtained from the FDA meeting minutes, the FDA had the following recommendations regarding the reporting of ECG data from the various clinical sources (the data should be tabulated by parameter, PR interval data should be displayed for prolongations of ≤ 200 msec or ≥ 201 msec, QRS ≤ 100 msec and ≥ 101 msec, QT absolute ≥ 450 msec, and QTc ≤ 30 msec, ≥ 31 msec, ≤ 60 msec, ≥ 61 msec. At the request of the FDA, the sponsor stated that it would include some images from the study for the FDA to view in the planned submission.

October 21, 1999 A teleconference was held as a follow-up to the teleconference of October 13, 1999.

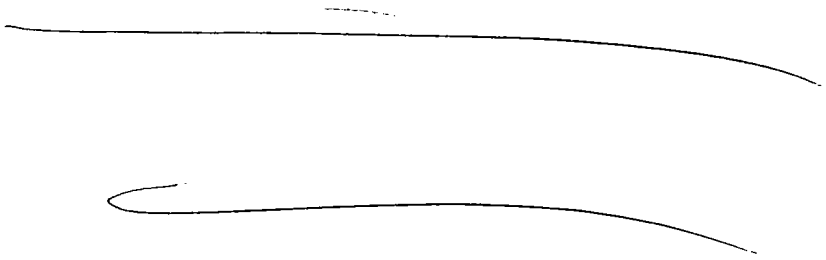
The reason for this T-con was to clarify the presentation of EKG data and the normal/abnormal range of parameters in the NDA.

For the PR Interval ≥ 201 msec
For the QRS Interval ≥ 101 msec
For the QTc/QT Interval ≥ 450 msec (post-dose with MultiHance)
For the QTc/QT change ≤ 30 msce, ≥ 31 msec, ≤ 60 msec, ≥ 61 msec from baseline (magnitude of change)

The FDA asked the sponsor to comment on the presence, change, appearance in either the T or U wave. For each patient that had prolongation of any parameters of the EKG, comments should be made that may be relevant (other parameters, vitals, medical history, medications, etc.).

April 27, 2001 The final statistical analysis plan in the NDA was dated November 6, 1997.

The primary assessment of efficacy was changed:



2. Foreign

As of April 1, 2001 MultiHance has been approved for marketing in 16 countries for CNS and Liver indications. Marketing authorization was first issued by the European Agency for the Evaluation of Medicinal Products (EMEA) on July 22, 1997.

The countries where MultiHance has been approved are listed in the following table.

Table #4 Foreign Approvals

Country	Approval Date
Austria	09-Nov-98
Belgium	01-Feb-99
Czech Republic	04-Oct-00
Germany	01-Sep-98
Denmark	26-Oct-98

Ireland	03-Apr-98
France	02-Jun-98
Greece	26-Aug-98
Italy	15-Oct-98
Israel	28-Sep-00
Luxembourg	28-Oct-98
The Netherlands	06-Jul-98
Portugal	27-Jul-00
Sweden	20-Nov-98
Finland	07-Dec-98
United Kingdom	22-Jul-97

List of countries where approval is pending:

Table #5 Pending Foreign Approvals

No country has withdrawn marketing approval of MultiHance. There are no known turn downs in other countries.

3. Pediatric

The sponsor has performed and presented two pediatric clinical trials. One trial was an open label, single center pharmacokinectic US trial (43,779-10) involving 25 pediatric healthy volunteer subjects using the 0.5M formulation and a 0.1 mmol/kg dose. The other trial was a double blind, randomized parallel-group multicenter European trial involving CNS patients using the 0.5M formulation and 0.1 mmol/kg dose. This trial also had a comparator (Magnevist) with 89 pediatric CNS patients using a 0.5M formulation and 0.1 mmol/kg dose.

D. Important Issues with Pharmacologically Related Agents

Magnevist has a similar osmolality and lower viscosity than MultiHance. Both are ionic and linear. Magnevist labeling contains a Warning that it is associated with serious vascular injection site reactions including compartment syndrome, phlebitis, thrombophlebitis, fasciitis, and amputations (reported in two patients). These adverse reactions have occurred at normal and increased rates of injection and volumes, with a wide age range of adults, with apparently normal to compromised vasculature. It is possible that the events are related to osmolality, ionicity, and/or viscosity.

MultiHance must, therefore, show sufficient evidence that it dose not have the same types of serious vascular injection site related adverse events.

II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Biopharmaceutics

Refer to the Biopharmaceutics report for a complete discussion of the multiple deficiencies, comments, and recommendations. Following is a brief summary of the important pre-clinical animal findings:

Histology
Vacuolization was found in the kidney, bladder, liver, pancreas, and testes.
Necrosis of the liver and increased organ weight was found (liver and kidney).
Moderate to severe local injection site reactions found with paravenous injections.
Laboratory Tests
Changes in urinary electrolyte levels were found
Changes in liver enzyme levels were found
ECG Evaluation
Lack of continuous ECG and complete QTc Interval assessments
Enzyme Induction and Metabolism
No evidence of metabolism was found for rats or dogs. In rats, no induction of hepatic metabolizing enzymes (including cytochrome P450, cytochrome b5, analine hydroxylase, aminopyrine N-demethylase, 7-ethoxycoumarin O-deethylase, and NADPH cytochrome c reductase) were found.
Blood Brain Barrier (BBB) - Does not cross the intact blood brain barrier
Carcinogenicity tests – none were performed
Mutagenicity tests - Found not mutagenic in vitro (Ames, genic, chromosome, DNA damage, unscheduled DNA synthesis tests) or in vivo (micronucleas test)

B. Chemistry

Generic Name	Gadobenate dimeglumine
Weight	529 mg
Osmolality	1.97 osmol/kg @ 37°C
Viscosity	5.3 mPas @ 37°C
Density	1.22 g/mL @ 20°C
pH	6.5 to 7.5
Ionicity	Ionic
Structure	

MultiHance is a hypertonic, clear, colorless aqueous solution composed of:
BOPTA
Meglamine
Water
No preservative, no buffer

MultiHance is supplied as:
5 mL single dose 10 mL vials
10 mL single dose 10 mL vials
15 mL single dose 20 mL vials
20 mL single dose 20 mL vials

C. Pharmacokinetics

Distribution half-life	0.085-0.605 hours
Metabolism	No detectable biotransformation
	Dissociation is minimal (<1% in feces)
Elimination	
Kidney (urine)	78-96%
Feces	
Half life	1.17-2.02 hours
Renal Impairment (0.2 mmol/kg)	
Elimination half life	
Moderate	6.1 hours
Severe	9.5 hours
Hemodialysis (0.2 mmol/kg)	
Elimination half life	
Dialysis	1.21 hours
Off-dialysis	42.4 hours
Hepatic Impairment (0.1 mmol/kg)	
No effect for Class B or C	

Adults
Sex had no effect (multiple regression analysis)
Age was not systematically studied
Race was not systematically studied
Drug-drug interactions
Not systematically studied

MO Comment: For dialysis patients, hemodialysis is required within [redacted] hours of the administration of MultiHance. The mechanism of hepatic uptake and fecal excretion is unclear.

D. Microbiology

There are no significant microbiological issues and they are recommending approval.

E. Statistics

The relevant results and conclusions are integrated into this review.

III. Human Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of MultiHance was evaluated in four studies that were performed in healthy volunteers (PT52E, PT58E, PT62E, and B19036/034) and four studies that were performed in special populations (43,779-4, 43,779-5, 43,779-8, and 43,779-10). This section will evaluate the pharmacokinetics of the special population studies, however, the safety of these studies will be discussed in greater detail in the section on special populations.

MultiHance was administered in doses ranging from 0.005 mmol/kg of the 0.25 M formulation (PT52E and PT58E) to 0.4 mmol/kg of the 0.5 M formulation (PT62E). The four healthy volunteer studies included a total of 54 male subjects, 40 of which received a single dose of MultiHance and 14 received placebo.

MultiHance undergoes rapid distribution and elimination with an estimated distribution half-life in the range of 0.08 to 0.61 hours and an estimated elimination half-life in the range of 1.2 to 2 hours in subjects with normal renal function. Total body clearance (CL) was also rapid with estimates ranging from 0.093 L/hr/kg to 0.133 L/hr.kg. The volume of distribution approximates the extracellular fluid volume. MultiHance is predominantly excreted unchanged into the urine (78%-96%) with fecal elimination ——— occurring to a much lesser extent. It does not show measurable binding to human serum albumin and does not undergo metabolism via hepatic drug metabolizing enzymes. There does not appear to be an appreciable effect of MultiHance on iron excretion into the urine, however, urinary excretion of zinc increased in subjects taking MultiHance. The sponsor did not specifically study the effect of MultiHance on serum ionic and total calcium, copper, or manganese.

A. Renal Impairment and Dialysis

Studies 43,779-4 and 43,779-5

These two US studies evaluated the effect of a 0.2 mmol/kg dose of 0.5 M MultiHance on 20 patients with renal impairment and 11 patients on dialysis, respectively.

In subjects with renal impairment (9 patients with moderate = CrCL from 30 to ≤60 mL/min and 11 patients with severe = CrCL from 10 to ≤30 mL/min), the elimination half-life is prolonged (from 2.0 hours to 6.1 hours or to 9.5 hours for moderate or severe renal impairment, respectively), and renal clearance and total body clearance decrease as renal function decreases (see Table #6 below). As renal function decreases, there is a corresponding mild increase in fecal elimination of gadolinium.

In 11 subjects requiring hemodialysis (performed approximately 30 minutes post-dose), the elimination half-life is markedly prolonged off dialysis (43.4 hours) compared to with dialysis (1.2 hours). MultiHance's gadolinium is readily dialyzable which is confirmed with the mean % of administered dose of Gd found in the dialysate fluid (72%) being