CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-357

21-358

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA 21-357 (Single-dose) NDA 21-358 (Multi-dose)

Brand Name: MultiHance

Generic Name: Gadobenate dimeglumine

Sponsor: Bracco Diagnostics, Inc.
P.O. Box 5225 Princeton, NJ 08543-5225

Recommended Doses: ***(From the sponsor's submission)***

Central Nervous System

Adults

The recommended dose of MultiHance is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion or bolus injection.

Dosage form and strength:

529 mg/mL (0.5M) gadobenate dimeglumine solution supplied as:
5 and 10 mL single dose 10 mL vials
15 and 20 mL single dose 20 mL vials
50 and 100 mL Pharmacy Bulk Packages (Bulk Packages)

Indications:

"*MultiHance is indicated for intravenous use in adults an adjunct to magnetic resonance imaging (MRI) of the Central Nervous System (brain, spine, and surrounding structures).*"

Submission Date: 27 April 2001

Assigned Date: 02 May 2001

Review Date: 22 February, 2002

Reviewer: Hyun Kim, Ph.D.

Team Leader: John Hunt, Deputy Director

I. EXECUTIVE SUMMARY

MultiHance is a paramagnetic contrast imaging agent that has been developed for ——— use in magnetic resonance imaging (MRI). The active ingredient of the MultiHance formulation is gadobenate dimeglumine. As of April 1, 2001 MultiHance has been approved for marketing in 16 countries for Central Nervous System (CNS) and Liver indications. MultiHance ——— in Japan and South Africa.

Bracco Diagnostics, Inc. has submitted two MultiHance NDAs for the use of Gadolinium as a signal enhancing agent for intravenous use in: 1) adults ——— as an adjunct to MRI of the Central Nervous System and 2) ——— The following eight studies were included in item 6 (Human Pharmacokinetics and Bioavailability section) of NDA 21-357 and cross referenced for NDA 21-358.

	Agent/Placebo	Dose (single dose)
4 Healthy Volunteers	40/14	0.005 – 0.4 mmol/kg
1 Renally impaired	20/12	0.2 mmol/kg
1 Hemodialysis	11/6	0.2 mmol/kg
1 Impaired Hepatic Function	11/5	0.1 mmol/kg
1 Pediatric (2 - <16 years old)	25/0	0.1 mmol/kg
Total subjects = 144	Males = 112; Female = 32	

Healthy Volunteers (Safety and Pharmacokinetics):

Four single-dose intravenous studies (PT52E, PT58E, PT62E and B19036/034) were conducted in 54 healthy male subjects (40 received the agent and 14 received placebo) to assess the pharmacokinetics of gadobenate dimeglumine. The doses administered in these studies ranged from 0.005 to 0.4 mmol/kg. Plasma concentrations and area-under-the-curve (AUC) demonstrate linear pharmacokinetics over this dosing range. Total body clearance and renal clearance (averaging a period of 0 – 4 hours after dosing) were essentially constant across the dosage range studied (independent of dose). The pharmacokinetics of gadobenate ion following intravenous administration is described using a two-compartment model. Gadobenate ion has a rapid distribution half life (reported as mean ± SD) of 0.085 ± 0.004 to 0.605 ± 0.072 hours, and an elimination half life that ranges from 1.17 ± 0.26 to 2.02 ± 0.60 hours across studies. Gadobenate ion is eliminated predominately via the kidneys, with 78% to 96% of an administered dose recovered in the urine while up to 7.2% is eliminated via the biliary route and recovered in feces (*i.e.*, 0% - 7.2% (PT52E), 0.6% - 3.5% (PT62E) and <0.03% to 3.65% (B19036/034)).

Collected plasma and urine samples were assayed with HPLC and fecal samples were assayed with XRF (PT52E and PT62E) and HPLC (B19036/034). For MultiHance, for the CNS indication, repeat dose administration is to be allowed. However, because the pharmacokinetics of MultiHance are independent of dose (*i.e.*, up to a dose of 0.4 mmol/kg) and the maximum dosage would only be 0.2 mmol/kg if two separate administrations are given, no multiple dose pharmacokinetic study is needed.

Studies that were conducted in special populations included the following.

Renal Impairment:

A single intravenous dose of 0.2 mmol/kg of MutiHance was administered to 20 subjects with impaired renal function (6 men and 3 women with moderate renal impairment [urine creatinine clearance >30 to <60 mL/min] and 5 men and 6 women with severe renal impairment [urine creatinine clearance >10 to

<30 mL/min]). The mean (±SD) renal clearances (CL_r) were 0.143 (0.021), 0.039 (0.024), and 0.015 (0.005) L/hr/kg for the normal renal function, moderate, and severe renal impairment groups, respectively. Furthermore, estimates of the terminal elimination half life ($t_{1/2}$) were 1.96 (0.16), 6.11 (2.95), and 9.48 (3.48) hr for the normal renal function, moderate, and severe renal impairment groups, respectively. For this [redacted] product, based on the observed dose ranging data up to 0.4 mmol/kg and the recommended single dose 0.1 mmol/kg being only for CNS patients, dose adjustments for patients with reduced renal clearance is probably not necessary based on pharmacokinetics.

Hemodialysis:

A single intravenous dose of 0.2 mmol/kg of MutiHance was administered to 11 subjects (5 males and 6 females) with end-stage renal disease requiring hemodialysis to determine the pharmacokinetics and dialyzability of gadobenate. Dialysis was performed approximately 30 minutes after the administration of study drug. Comparison of the elimination half life during the dialysis period with the elimination half life of the off-dialysis period showed an approximately 35 fold increase in half-live, with a mean value of 1.21 hours versus 42.4 hours. Dialysate fluid collected during dialysis accounted for a mean of 72% of the administered dose. These results show that gadobenate is dialyzable. Because of these findings, a caution statement is being requested to be added to the hemodialysis section of the labeling.

Hepatic Impairment:

A single intravenous dose of 0.1 mmol/kg of MutiHance was administered to 11 subjects (8 males and 3 females) with impaired liver function (Class B or C modified Child-Pugh Classification). Mean estimates of total clearance were 1.58 and 1.28 L/hr/kg and mean estimates of renal clearance were 0.143 (0.021) and 0.106 (0.052) L/hr/kg for the normal volunteers and impaired hepatic function group, respectively. Furthermore, estimates of the terminal elimination half lives ($t_{1/2}$) were 1.96 (0.16), and 2.06 (0.91) hr for the healthy male volunteers and impaired hepatic function group, respectively. With only small amounts of gadobenate being eliminated via biliary/fecal excretion (up to 7.2%), plus the results of this study indicating little change in the pharmacokinetics of gadobenate in hepatically impaired patients, no dose adjustment is probably warranted for this patient population knowing they would only be exposed to one or two doses.

[redacted]

COMMENTS TO THE SPONSOR:

1. A pharmacokinetic and safety study is necessary in children in the age range covering

2. Please reanalyze the available adult pharmacokinetic data as a function of age and as a function of gender.

3.

4. Due to the increased half life of MultiHance in patients requiring hemodialysis, patients should have his/her hemodialysis done in a timely manner following MultiHance administration to decrease patient's total exposure time to the agent.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) has reviewed the information and data submitted 27 April 2001 for NDA 21-357. NDA 21-358 for MultiHance (Multi-dose) which is a pharmacy bulk pack, was also submitted 27 April 2001. Since this pharmacy bulk pack did not contain any new clinical pharmacokinetic data, the same information applies to this NDA as NDA 21-357.

Based on the review of the information and data submitted under item 6 (Human Pharmacokinetics and Bioavailability) for the two NDAs, OCPB/DPE II finds them overall acceptable to support the Agency's Bioavailability and Bioequivalence Regulations (21 CFR 320). However, additional information as covered under comment Nos. 1, 2 and 3 of the section above titled 'Comments to the Sponsor' should be communicated and addressed by the sponsor. Comment No.4 should also be communicated to the sponsor as appropriate

OCPB/DPE II is of the opinion that the requested information should be obtained and addressed by the drug sponsor prior to NDA approval. However, if the application is found to be approvable the requested information could be obtained post-approval. Additionally, the labeling changes as covered under section V (pages 12 – 16) should be communicated to the sponsor.

/S/

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III. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

HEALTHY VOLUNTEER STUDIES (Safety, and Pharmacokinetics) (Studies PT52E, PT58E, PT62E and B19036/034)

Total subjects = 54 males Drug received = 40, Placebo = 14
Dose range = 0.005 mmol/kg – 0.4 mmol/kg; single-dose
Plasma, urine and feces were collected.
Plasma and urine samples were assayed with HPLC
Fecal samples were assayed with XRF (PT52E and PT62E) and HPLC (B19036/034)

Four studies were conducted in healthy, male volunteers to evaluate the pharmacokinetics and safety of intravenously administered doses of MultiHance. Administered doses ranged from 0.005 mmol/kg of the 0.25M solution (Study PT52E) to 0.4 mmol/kg of the 0.5M solution (Study PT62E). In Study PT58E individual pharmacokinetic parameters could not be determined due to insufficient sampling points. In the three studies in which pharmacokinetic parameters could be determined, the data were best fit using a two-compartment model.

Gadobenate is rapidly eliminated from the body with a terminal elimination half lives ranging from 1.17 to 2.02 hr. Total body clearance (CL) was also rapid with estimates ranging from 0.093 L/hr/kg to 0.133 L/hr/kg.

Linear regression analysis of renal clearance (over a 0 to 240 minute period after dosing) versus dose demonstrated a linear relationship. This indicates that renal clearance (CLr) is constant across the dosage range studied. For the three studies for which pharmacokinetic parameters were calculated, the mean percent of administered dose recovered in the urine per dose level ranged from 78% to 98%. Fecal elimination was up to 7.2% of the administered dose. From this data, it is clear that elimination of gadobenate is dominated by urinary excretion.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Moderate to Severe renal Impaired Patients (Study 43,779-4)

(Moderate 30 to ≤60 mL/min and Severe 10 to ≤30 mL/min)

Total patients	= 32	23 males and 9 females
0.2 mmol/kg	= 20	(9 moderate and 11 severe)
Placebo	= 12	

Renal impairment was shown to affect the elimination of gadolinium. Estimates of the terminal elimination half-lives were 2.0, 6.1 and 9.5 hr for the normal renal function, moderate, and severe renal impairment groups, respectively. This indicates that the terminal elimination half life of MultiHance will be longer in subjects with renal impairment, and the increase in the half life is greater when renal impairment is more severe. Confirmation of this effect was given by the estimates of CL which were 0.158, 0.041, and 0.021 L/hr/kg for the normal renal function, moderate and severe renal impairment groups, respectively.

Mean cumulative urinary excretion up to 160 hours post dose was similar for the moderate and severe renal impairment groups at 74% and 69%, respectively. In feces, mean cumulative excretion of gadolinium was higher in subjects with renal impairment when compared with healthy volunteers, with mean values of 1.9%, 5.6%, and 7.7% for the normal renal function, moderate and severe renal

impairment groups, respectively. This suggests that as renal function decreases there is a corresponding slight increase in the fecal elimination of gadolinium.

Hemodialysis Patients (Study 43,779-5)

Total patients	= 17	9 males and 8 females
0.2 mmol/kg	= 11	(5 males and 6 females)
Placebo	= 6	

Dialysis was performed approximately 30 minutes post dose.
Elimination half-live is estimated to be 35-fold that of normal renal function (1.21 hours as compared with 42.4 hours).
Dialysis session accounted for a mean of 72% of the administered dose. These results show that gadolinium is dialyzable.

Hepatic Impaired Patients (Study 43,779-8)

Total patients	= 16	12 males and 4 females
0.1 mmol/kg	= 11	
Placebo	= 5	

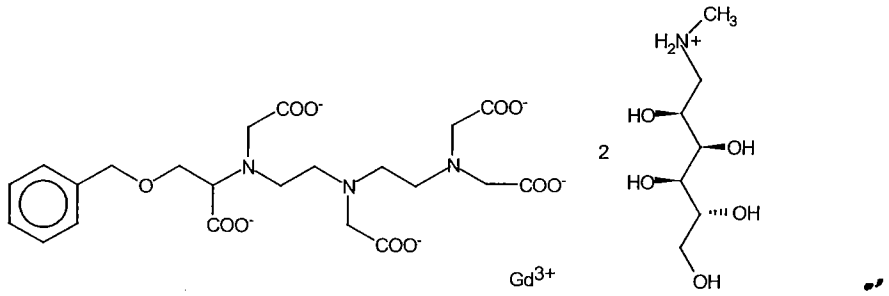
The terminal elimination half-lives were 1.81 (normal) and 2.06 (impaired) hours.
Total body clearance values were 0.158 (normal), and 0.128 (hepatically impaired) L/hr/kg, and mean estimates of CL_r were 0.143 and 0.106 L/hr/kg for normal subjects and hepatically impaired, respectively.

[redacted]

IV. QUESTION BASED REVIEW

What is the description of the product?

MultiHance for injection is supplied as a sterile, non-pyrogenic, clear, colorless aqueous solution intended for intravenous use only. MultiHance has an osmolality 6.9 times that of plasma (2.85 mOsmol/kg water) and is hypertonic under conditions of use. MultiHance contains no preservatives.



pH	6.5-7.5
Osmolality	1.970 osmol/kg @ 37 °C
Viscosity	5.3 mPas @ 37 °C
Density @ 20 °C	1.220 g/mL

Gadobenate dimeglumine is chemically designated as (4*RS*)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)] gadolinate(2-) dihydrogen compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2) with a molecular weight of 1058.2 and an emperical formula of $C_{22}H_{28}GdN_3O_{11} \bullet 2C_7H_{17}NO_5$.

How is it supplied?

529 mg/mL (0.5M) gadobenate dimeglumine solution

Five 5 mL single dose 10 mL vials
Five 10 mL single dose 10 mL vials
Five 15 mL single dose 20 mL vials
Five 20 mL single dose 20 mL vials
Five 50 mL Pharmacy Bulk Packages (Bulk Packages)
Five 100 mL Pharmacy Bulk Packages (Bulk Packages)

(0.25M or 0.5M solution of MultiHance [provided by Bracco SpA, Milan, Italy] was used for the studies)

What is the proposed dose?

Central Nervous System

Adults

The recommended dose of MultiHance is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion or bolus injection.

[redacted]

Is there any special safety concerns for this product?

In the adult populations, there were sufficient data provided for clinical pharmacokinetic evaluation for any unusual events with the agent.

[redacted]

What is the excretion of zinc?

Since gadolinium is known to be mutagenic and the level of zinc in the urine is an indirect indication of how much gadolinium is left in the body, it is desirable to have a minimum amount of zinc excreted in the urine.

In healthy male subjects [redacted] of zinc was excreted in the urine in the three hour period post dose. Alternatively, there was up to a 5 fold increase of zinc excretion in the urine in the 24 hour period post dose for both moderate and severe renally impaired subjects when compared to subjects who received placebo suggesting greater retention of gadolinium in subjects with decreased renal function.

What is the pharmacokinetic profile for this product?

Distribution half life is in the range of 0.08 to 0.61 hours
Terminal elimination half lives range from 1.17 hours to 2.02 hours
Fecal elimination ranged from 0% - 7.2% of the administered dose.
See figures 1 and 2.

Are there known drug-drug interactions?

No data was submitted.

What is the stability of the chelating agent (BOPTA) in vivo?

The chelating agent, BOPTA, was assayed in plasma, urine, and feces. The results of the assays showed that the cumulative percent of the injected dose eliminated in the urine and in the feces as BOPTA, was between 1.5% to 2.3% for urine and less than 0.71% for feces.

Are there similar FDA approved products?

Trade Name	Magnevist	Prohance	Omniscan	Optimark
Dosage	0.1 mmol/kg	0.1 mmol/kg	0.1 mmol/kg	0.1 mmol/kg
Structure	Linear	Macrocyclic	Linear	Linear

V. Labeling

NOTE: Only portions of the proposed label requiring comments or changes are presented in this section. Proposed changes are in **black bold type**.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Three single-dose intravenous studies were conducted in 32 healthy male subjects to assess the pharmacokinetics of gadobenate dimeglumine. The doses administered in these studies ranged from 0.005 to 0.4 mmol/kg. Upon injection, the meglumine salt is completely dissociated from the gadobenate dimeglumine complex. Thus, the pharmacokinetics is based on the assay of gadobenate ion, the MRI contrast effective ion in gadobenate dimeglumine. Data for plasma concentration and area under the curve demonstrated linear dependence on the administered dose. The pharmacokinetics of gadobenate ion following intravenous administration can be best described using a two-compartment model.

Distribution: Gadobenate ion has a rapid distribution half-life (reported as mean ± SD) of [redacted] 4 to 0.605 ± 0.072 hours. Volume of distribution of the central compartment ranged from 0.074 ± 0.017 to 0.158 ± 0.038 L/kg, and estimates of volume of distribution by area ranged from 0.170 ± 0.016 to 0.282 ± 0.079 L/kg. These latter estimates are approximately equivalent to the average volume of extracellular body water in man. In vitro study showed no appreciable binding of gadobenate ion to human serum proteins.

Metabolism: There was no detectable biotransformation of gadobenate ion. Dissociation of gadobenate ion *in vivo* has been shown to be minimal, with less than 1% of the free chelating agent being recovered alone in feces.

Elimination: Gadobenate ion is eliminated predominately via the kidneys, with 78% to 96% of an administered dose recovered in the urine. Total plasma clearance and renal clearance estimates of gadobenate ion were similar, ranging from 0.093 ± 0.010 to 0.133 ± 0.270 L/hr/kg and 0.082 ± 0.007 to 0.104 ± 0.039 L/hr/kg, respectively. The clearance is similar to that of substances that are subject to glomerular filtration. The mean elimination half-life ranged from 1.17 ± 0.26 to 2.02 ± 0.60 hours. A small percentage of the administered dose (0.6% to 4%) is eliminated via the biliary route and recovered in feces.

Pharmacokinetics in Special Populations

Renal Impairment: A single intravenous dose of 0.2 mmol/kg of MULTIHANCE was administered to 20 subjects with impaired renal function (6 men and 3 women with moderate renal impairment [urine creatinine clearance >30 to <60 mL/min] and 5 men and 6 women with severe renal impairment [urine creatinine clearance >10 to <30 mL/min]). [redacted] Mean estimates of the elimination half-life were 6.1 ±3.0 and 9.5 ± 3.1 hours for the moderate and severe renal impairment groups, respectively as compared with 1 to 2 hours in healthy volunteers.

Hemodialysis: A single intravenous dose of 0.2 mmol/kg of MULTIHANCE was administered to 11 subjects (5 males and 6 females) with end-stage renal disease requiring hemodialysis to determine the pharmacokinetics and dialyzability of gadobenate. Approximately 72% of the dose were recovered by hemodialysis over a 4-hour period. The mean elimination half-life on dialysis was 1.21 ± 0.29 hours as compared with 42.4 ± 24.4 hours when off dialysis. [redacted]

Hepatic Impairment: A single intravenous dose of 0.1 mmol/kg of MULTIHANCE was administered to 11 subjects (8 males and 3 females) with impaired liver function (Class B or C modified Child-Pugh Classification). Hepatic

impairment had little effect on the pharmacokinetics of MULTIHANCE with the parameters being similar to those calculated for healthy subjects.

A multiple regression analysis performed using pooled data from several pharmacokinetic studies found no significant effect of sex upon the pharmacokinetics of gadobenate.

Age: Pharmacokinetic differences for elderly and younger patients have not been systematically studied after intravenous administration of MULTIHANCE.

Race: Pharmacokinetic differences due to race have not been systematically studied.

Drug-Drug Interactions: Drug interactions have not been

VI. Appendices

Table 1: Summary of Clinical trials

Protocol Number	Study Design	Indication (s)	Dose # of Subjects	Comments
PT52E	Single-Blind, Single Ascending Dose, Placebo Controlled Single-Center	Dose Escalation on Healthy Male Volunteers (Adult)	**0.25 M** 0.005 mmol/kg 4 0.05 mmol/kg 4 0.1 mmol/kg 4 0.2 mmol/kg 4 Placebo 8	**Pharmacokinetics:** Plasma, urine, feces Up to 96 hrs postdose **Safety:** Adverse events, vital signs, laboratory tests, ECG
PT62E	Single-Blind, Single Ascending Dose, Placebo Controlled Single-Center	Dose Escalation on Healthy Male Volunteers (Adult)	**0.5 M** 0.2 mmol/kg 4 0.3 mmol/kg 4 0.4 mmol/kg 4 Placebo 6	**Pharmacokinetics:** Plasma, urine, feces Up to 96 hrs postdose **Safety:** Adverse events, vital signs; laboratory tests, ECG, tolerability
B19036/034	Open-Label, Single Dose, Single-Center	Healthy Male Volunteers (Adult)	**0.5 M** 0.3 mmol/kg 4	**Pharmacokinetics:** Plasma, urine, feces Up to 48 hrs postdose **Safety:** Adverse events, vital signs, laboratory tests, ECG, PE
PT58E	Open-Label, Single Ascending Dose, Non-Randomized, Single-Center	Healthy Male Volunteers (Adult)	**0.25 M** 0.005 mmol/kg 2 0.05 mmol/kg 2 0.1 mmol/kg 2 0.2 mmol/kg 2	**Pharmacokinetics:** Plasma, urine Up to 48 hrs postdose **Safety:** Adverse events, vital signs, laboratory tests, ECG
43,779-4	Double-Blind, Randomized, Placebo-Controlled, Multi-Center	Renally Impaired Subjects (Adults)	**0.5 M** 0.2 mmol/kg 20 Placebo 12	**Pharmacokinetics:** Gd levels determined from blood, urine and feces. Zn and Fe excretion determined from urine **Safety:** Adverse events, vital signs, laboratory tests, ECG, PE
43,779-5	Double-Blind, Parallel, Randomized, Placebo-Controlled, Single-Center	ESRD Patients requiring Hemodialysis (Adults)	**0.5 M** 0.2 mmol/kg 11 Placebo 6	**Pharmacokinetics:** Plasma collected up to 24 hrs postdose. dialysis performed 30 min after study agent administration **Safety:** Adverse events, vital signs, ECG, Fe metabolism, laboratory tests, PE
43,779-8	Double-Blind, Parallel, Randomized, Placebo-Controlled, Single-Center	Liver Impaired Subjects (Adults)	**0.5 M** 0.1 mmol/kg 11 Placebo 5	**Pharmacokinetics:** Gd levels determined from blood and urine **Safety:** Adverse events, vital signs, ECG, Fe metabolism, laboratory tests, PE
43,779-10	Open-Label, Single-Center	Healthy Children (Pediatric)	**0.5 M** 0.1 mmol/kg 25	**Pharmacokinetics:** Gd levels determined from blood and urine **Safety:** Adverse events, vital signs, ECG, laboratory tests, PE

Healthy Volunteers Studies (Safety, Effectiveness and Pharmacokinetics)
4 studies PT52E, PT58E, PT62E and B19036/034
Total subjects = 54 (males only)
Drug received = 40, Placebo = 14
Dose range = 0.005 mmol/kg – 0.4 mmol/kg single-dose
Plasma, Urine and Feces were collected
Plasma and Urine were assayed with HPLC
Feces were assayed with XRF (PT52E and PT62E) and HPLC (B19036/034)
Distribution half lives in the range of 0.08 to 0.61 hours
Terminal elimination half lives ranging from 1.17 hours to 2.02 hours
Linear regression analysis of renal clearance in the period of 0 – 4 hours after dosing versus dose demonstrated a linear relationship; in this period. This indicates that renal clearance is constant across the dosage range studied (independent of dose).
Fecal elimination ranged from 0 - 7.2% of the administered dose.

Four studies were conducted in healthy, male volunteers to evaluate the pharmacokinetics and safety of intravenously administered doses of MultiHance (dose-ranging studies). One study (PT58E) was not used for the evaluation because only 5 postdose blood samples per individual were obtained, and thus individual pharmacokinetic parameters could not be determined. In the remaining studies (PT52E, PT62E, and B19036/034), pharmacokinetic parameters were determined using compartmental methods. Gadobenate has mean terminal elimination half-lives ranging from 1.17 hours to 2.02 hours. Total body clearance was also rapid with mean estimates ranging from 0.093 L/hr/kg to 0.133 L/hr/kg. Fecal elimination ranged from 0 to 7.2% of the administered dose.

PT52E (B19036/7) Safety and Pharmacokinetics on Healthy Volunteers
Single-blind, single-dose, placebo-controlled, ascending dose, single-center study. **[0.25M]**
IV injection at a rate of 10 mL/min, volume of 1-64 mL depending on dose level.
N = 24 all males 16 received study drug and 8 received placebo.

0.005 mmol/kg	= 4
0.05 mmol/kg	= 4
0.1 mmol/kg	= 4
0.2 mmol/kg	= 4
Placebo	= 8

Age from 18 - 50 years old, Mean age = 29.0
Weight from 50.3 - 87.5 kg, Mean weight = 70.7
Plasma, Urine and Feces collected up to 96 hours post dose.

Mean Plasma concentration – time profiles for each dose level of MultiHance administered to healthy volunteers

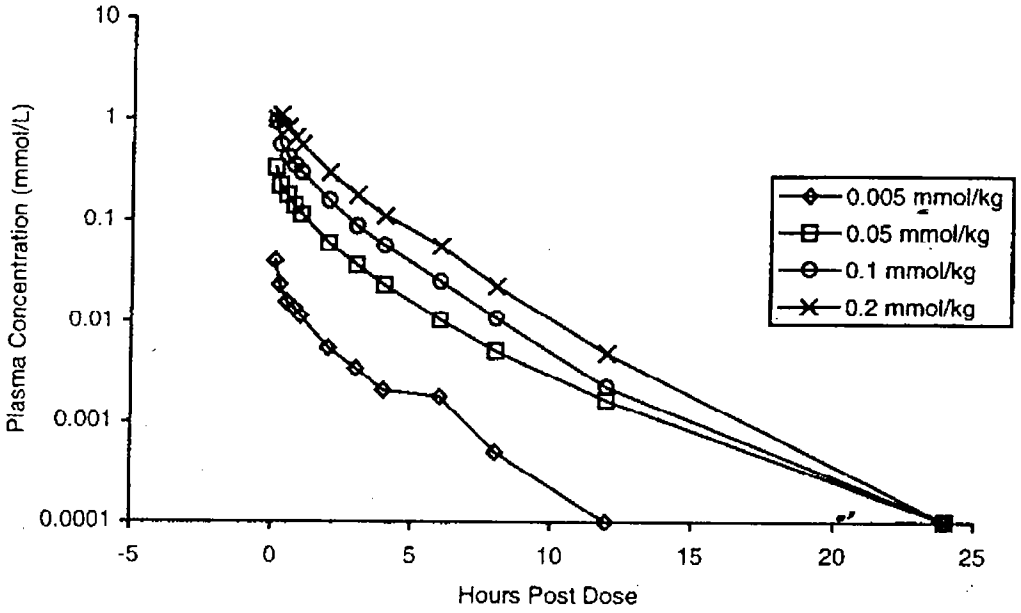


Fig.1 PT52E (0.005 mmol/kg to 0.2 mmol/kg [0.25M])

Mean Plasma concentration – time profiles for each dose level of MultiHance administered to healthy volunteers

Table. 2 PK summary of study PT52E

Study Number[a]	Route of Administration	Dose mmol/kg	Analyte	Vc (L/kg)	Vd_{area} (L/kg)	Vd (L/kg)	Vdss (L/kg)	$AUC_{0-\infty}$ (mg•hr/L)	t½ (hr)	Cl (L/hr/kg)	Cl_r (L/hr/kg)	Percent of Dose Eliminated via the Kidneys[b]
PT52E	IV injection at a rate of 10 mL/min, volume of 1 – 64 mL depending on dose level.	0.25M MULTIHANCE 0.005 mmol/kg	Gadobenate in plasma	0.082 (0.012)	0.216 (0.014)	ND	ND	25.8 (4.4)	1.17 (0.26)	0.133 (0.270)	0.104 (0.039)	78.2 (64.0 – 96.2)
		0.25M MULTIHANCE 0.05 mmol/kg	Gadobenate in plasma	0.107 (0.015)	0.218 (0.008)	ND	ND	266 (20)	1.21 (0.12)	0.126 (0.009)	0.088 (0.031)	84.3 (46.0 – 115)
		0.25M MULTIHANCE 0.1 mmol/kg	Gadobenate in plasma	0.074 (0.017)	0.170 (0.016)	ND	ND	685 (75)	1.21 (0.09)	0.098 (0.011)	0.082 (0.007)	85.8 (78.8 – 90.6)
		0.25M MULTIHANCE 0.2 mmol/kg	Gadobenate in plasma	0.142 (0.032)	0.248 (0.016)	ND	ND	1299 (125)	1.68 (0.16)	0.104 (0.009)	0.093 (0.011)	93.6 (90.2 – 95.1)

PT58E (B19036-7) Safety and Effectiveness on Healthy Volunteers (MRI techniques)
Single-dose, open-label, ascending dose, single-center study. **[0.25M]**
IV injection at a rate of 10 mL/min, volume of 1.3 – 68 mL depending on dose level.
N = 8 all males 0.005 mmol/kg = 2
0.05 mmol/kg = 2
0.1 mmol/kg = 2
0.2 mmol/kg = 2
Age from 20 - 36 years old, Mean age = 28.0
Weight from 60.8 – 86.4 kg, Mean weight = 70.7
Plasma and Urine collected up to 48 hours post dose.

In this study, only 5 post-dose blood samples per individual were obtained (65,110, 360, 720, and 1440 minutes post-dose), and thus individual pharmacokinetic parameters could not be determined.

PT62E (B19036/7) Safety, Tolerance and Pharmacokinetics on Healthy Volunteers.
Single-blind, placebo-controlled, ascending dose, single-center study. **[0.5M]**
IV injection at a rate of 10 mL/min, volume of 24 – 60 mL depending on dose level.
N = 18 all males 12 received study drug and 6 received placebo.
0.2 mmol/kg = 4
0.3 mmol/kg = 4
0.4 mmol/kg = 4
Placebo = 6
Age from 18 - 50 years old, Mean age = 33.9
Weight from 56.0 – 79.8 kg, Mean weight = 70.0
Plasma, Urine and Feces collected up to 96 hours post dose.

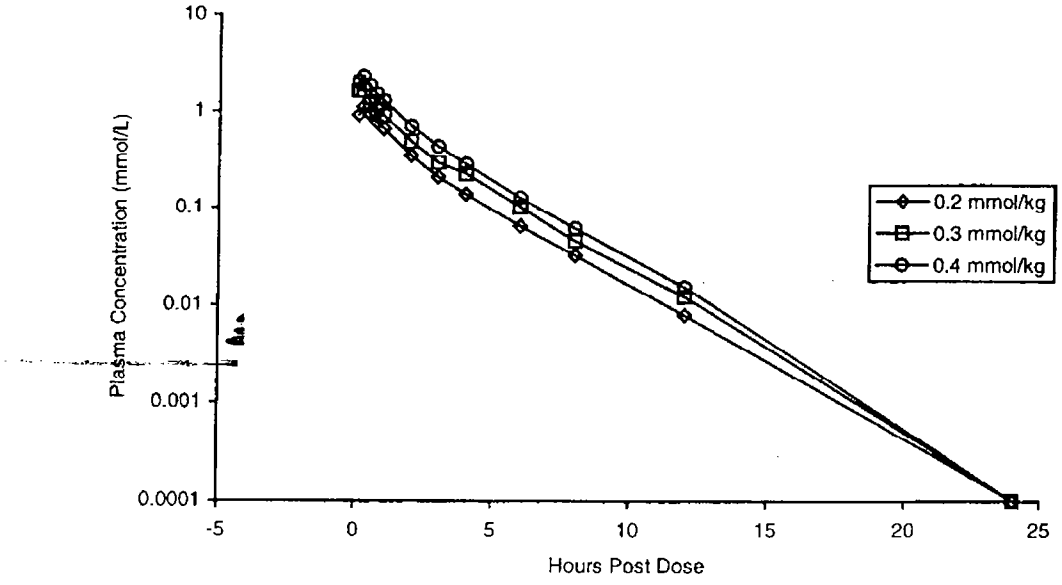


Fig.2 PT62E (0.2 mmol/kg to 0.4 mmol/kg [0.5M])
Mean Plasma concentration – time profiles for each dose level of MultiHance administered to healthy volunteers

Table. 3 PK summary of study PT62E

Study Number[c]	Route of Administration	Dose mmol/kg	Analyte	Vc (L/kg)	Vd_{area} (L/kg)	Vd (L/kg)	Vdss (L/kg)	$AUC_{0-\infty}$ (mg•hr/L)	t½ (hr)	CL (L/hr/kg)	CL_r (L/hr/kg)	Percent of Dose Eliminated via the Kidneys[b]
PT62E	IV injection at a rate of 10 mL/min, volume of 24 – 60 mL depending on dose level.	0.5M MULTIHANCE 0.2 mmol/kg	Gadobenate in plasma	0.158 (0.038)	0.262 (0.034)	ND	ND	2.19[a] (0.41)	1.96 (0.16)	0.094 (0.019)	0.082 (0.022)	86.8 (75.5 – 93.4)
		0.5M MULTIHANCE 0.3 mmol/kg	Gadobenate in plasma	0.147 (0.017)	0.282 (0.079)	ND	ND	3.11[a] (0.43)	2.02 (0.60)	0.098 (0.014)	0.090 (0.014)	91.3 (80.2 – 97.8)
		0.5M MULTIHANCE 0.4 mmol/kg	Gadobenate in plasma	0.149 (0.021)	0.261 (0.024)	ND	ND	4.34[a] (0.42)	1.95 (0.12)	0.093 (0.010)	0.089 (0.009)	95.6 (94.7 – 96.2)

Unit stated by the sponsor is incorrect for $AUC_{0-\infty}$

B19036/034 Fixed Dose (0.3 mmol/kg) Pharmacokinetics on Healthy Volunteers
Single-dose, open-label, single-center study. **[0.5M]**
IV injection at a rate of 10 mL/min, volume of 37 – 48 mL.
N = 4 all male 0.3 mmol/kg = 4
Age from 19 - 32 years old, Mean age = 26.5
Weight from 61.6 – 79.6 kg, Mean weight = 73.6
Plasma, Urine and Feces collected up to 48 hours post dose.

Table. 4 PK summary of study B19036/034

Study Number[c]	Route of Administration	Dose mmol/kg	Analyte	Vc (L/kg)	Vd_{area} (L/kg)	Vd (L/kg)	Vdss (L/kg)	$AUC_{0-\infty}$ (mg•hr/L)	t½ (hr)	CL (L/hr/kg)	CL_r (L/hr/kg)	Percent of Dose Eliminated via the Kidneys[b]
B19036/034	IV injection at a rate of 10 mL/min, volume of 37 – 48 mL.	0.5M MULTIHANCE 0.3 mmol/kg	Gadobenate in plasma	0.109 (0.032)	0.245 (0.018)	ND	0.208 (0.009)	3.19[a] (0.25)	1.81 (0.07)	0.095 (0.007)	0.086 (0.013)	90.0 (82.4 – 98.4)

Unit stated by the sponsor is incorrect for $AUC_{0-\infty}$

43,779-4 Safety and Pharmacokinetics on Renally – Impaired Patients
Double-blind, placebo-controlled, multi-center study. **[0.5M]**
IV injected over approx. 1 minute.
N = 32 23 males and 9 females.
0.2 mmol/kg = 20
Placebo = 12
Age from 34 – 84 years old, Mean age = 60.4*
Weight from 43 – 136 kg, Mean weight = 77.5*
Blood, urine and feces collected up to 48 hours post dose.
Iron and zinc levels determined from the Urine.
* *Only the patients who received MultiHance.*

This study was conducted to evaluate the pharmacokinetics of MultiHance in subjects with moderate or severe renal impairment. The degree of renal impairment was defined based upon an individual's

creatinine clearance (CrCL). Moderate renal impairment was defined as CrCL from 30 to $\leq$60 mL/min and severe renal impairment as Cr CL from 10 to $\leq$30 mL/min. Our guidance at the Food and drug administration defines as CrCL from 30 to $\leq$ 50 mL/min and severe renal impairment as Cr CL from 0 to $\leq$30 mL/min.

Table. 5 PK summary of study 43,779-4

Study Number[c]	Route of Administration	Dose mmol/kg	Analyte	Vc (L/kg)	Vd_{area} (L/kg)	Vd (L/kg)	Vdss (L/kg)	$AUC_{0-\infty}$ (mg•hr/L)	$t_{1/2}$ (hr)	CL (L/hr/kg)	CL_r (L/hr/kg)	Percent of Dose Eliminated via the Kidneys[b]
43,779-4	IV injection over approx. 1 minute.	0.5M MULTIHANCE 0.2 mmol/kg	Gadolinium in blood – moderate renal impairment	ND	ND	0.308 (0.069)	0.256 (0.060)	862 (392)	6.11 (2.95)	0.041[d] (0.018)	0.039[d] (0.024)	74.4 (46.1 – 92.9)
			Gadolinium in blood – severe renal impairment	ND	ND	0.277 (0.080)	0.221 (0.066)	1347 (366)	9.48 (3.08)	0.021[d] (0.005)	0.015[d] (0.005)	69.2 (53.2 – 96.5)

Renal impairment was shown to affect the elimination of gadolinium. Estimates of the terminal elimination half lives were 2.0, 6.1, and 9.5 hr for the normal renal function, moderate, and severe renal impairment groups, respectively. Also, clearances were 0.158, 0.041, and 0.021 L/hr/kg for the normal renal function, moderate, and severe renal impairment groups, respectively. Estimates of renal clearance were 0.143, 0.039, and 0.015 L/hr/kg for the normal renal function, moderate, and severe renal impairment groups, respectively. Vdss obtained from the non-compartmental

Table 6 Comparative PK summary of study 43,779-4

MEAN (SD) PHARMACOKINETIC PARAMETERS OF SUBJECTS WITH MODERATE OR SEVERE RENAL IMPAIRMENT AND SUBJECTS WITH NORMAL RENAL FUNCTION WHO RECEIVED *MULTIHANCE* AT A DOSE OF 0.2 MMOL/KG

	Degree of Renal Impairment		Normal Renal Function
Parameter Estimate	*Moderate* (CrCL from 30 to ≤ 60 mL/min)	*Severe* (CrCL from 10 to ≤ 30 mL/min)	*Historical Control* Group[b]
Vd (L/kg)	0.308 (0.069)	0.277 (0.080)	0.436 (0.057)[c]
Vdss (L/kg)	0.256 (0.060)	0.221 (0.066)	0.347 (0.015)[d,e]
$AUC_{0-\infty}$ (mcg (Gd) •hr/mL)	862 (392)	1347 (366)	NR[f]
CL (L/hr/kg)	0.041 (0.018)	0.021 (0.005)	0.158 (0.012)[e]
$t_{1/2}\lambda z$ (hr)	6.11 (2.95)	9.48 (3.08)	1.96 (0.16)
CL_r (L/hr/kg)	0.039 (0.024)	0.015 (0.005)	0.143 (0.021)[e]
% dose eliminated via the kidneys[a]	74.4 (46.1 – 92.9)	69.2 (53.2 – 96.5)	86.8 (75.5 93.4)
% dose eliminated in feces[a]	5.60 (1.87 – 11.8)	7.69 (2.06 15.3)	1.9 (0.6 – 2.8)

Abbreviations: Vd = volume of distribution, Vdss = volume of distribution at steady state, $AUC_{0-\infty}$ = area under the curve from time 0 to infinity, CL = total body clearance, $t_{1/2}\lambda z$ = terminal elimination half-life and CL_r = renal clearance, NR = not reported.

[a] Values presented are mean values (minimum – maximum). Gd = gadobenate.

[b] Data for the historical control group is derived from subjects in Study PT62E who were *healthy volunteers with normal renal* function who received MULTIHANCE at a dose of 0.2 mmol/kg.

[c] The volume parameter reported for the healthy volunteer group is Vd_{area}.

[d] Data for the historical control group is derived from subjects in Study B19036/034 who were healthy volunteers with normal renal function who received *MULTIHANCE at a dose of 0.3 mmol/kg* as Vdss was not measured in Study PT62E.

[e] These values have been adjusted from the original study using the factor of (1 – hematocrit) to account for the blood/plasma difference.

[f] The value for AUC for the control group is not reported here as the units are different from the units used in Study 43,779-4, thus it *is not possible to* make a comparison.

analysis, were 0.26L/kg for the moderate renal impairment group and 0.22 L/kg for the severe renal impairment group. These values of Vdss were comparable to the estimate of 0.35 L/kg obtained in healthy male volunteers with normal renal function. Mean cumulative urinary excretion in the period 0 to 160 hours after the dose was similar for the moderate and severe renal impairment groups at 74% and 69%, respectively. Mean cumulative excretion in feces was higher in subjects with renal impairment when compared with healthy male volunteers, with values of 1.9%, 5.6%, and 7.7% for the normal renal function, moderate, and severe renal impairment groups, respectively.

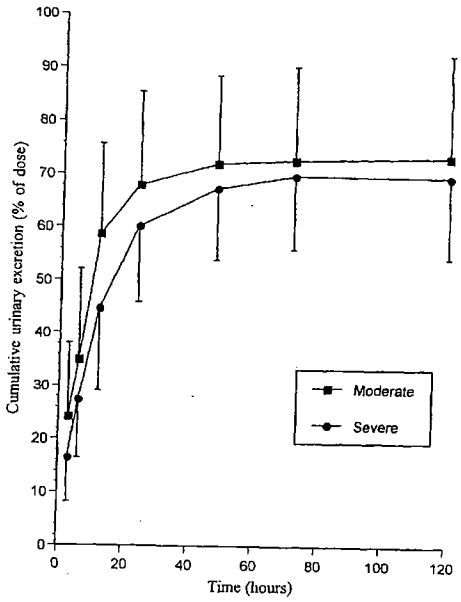


Fig. 3
Mean ±SD cumulative urinary excretion of gadolinium in moderate and severe renal impairment subjects.

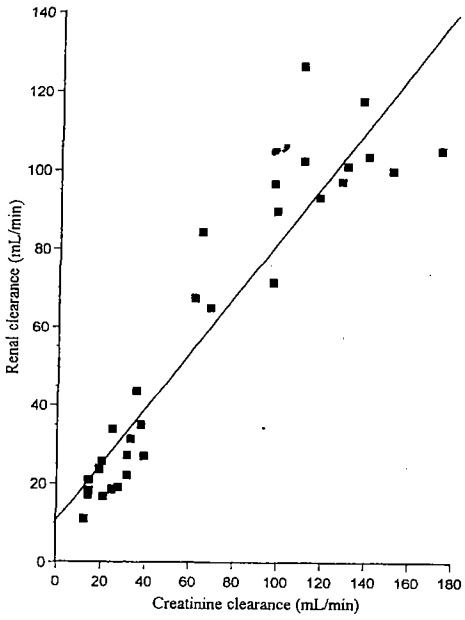


Fig. 4
Linear regression of renal clearance of MultiHance versus creatinine clearance for all subjects with renal impairment and of normal subjects

43,779-5 Safety and Dialyzability (PK) on ESRD Patients requiring Hemodialysis
Double-blind, placebo-controlled, single-center study. **[0.5M]**
IV injection over approx. 5 minutes.
N = 17 9 males and 8 females,
11 received study drug and 6 received placebo.
0.2 mmol/kg = 11
Placebo = 6
Age from 27 – 69 years old, Mean age = 41.7
Weight from 50 – 109 kg, Mean weight = 70.4
Plasma collected up to 30 hours post dose.

Table. 7 PK summary of study 43,779-5

Study Number[c]	Route of Administration	Dose mmol/kg	Analyte	Vc (L/kg)	Vd_{area} (L/kg)	Vd (L/kg)	Vdss (L/kg)	$AUC_{0-\infty}$ (mg•hr/L)	t½ (hr)	CL (L/hr/kg)	CL_r (L/hr/kg)	Percent of Dose Eliminated via the Kidneys[h]
43,779-5	Rapid IV bolus injection.	0.5M MULTIHANCE 0.2 mmol/kg	Gadolinium in blood and dialysate fluid	NA	NA	NA	NA	NA	42.4[e] (24.4) 1.21[f] (0.29)	NA	NA	72.1[g] (4.6)

This study was conducted to investigate the pharmacokinetics and safety of MultiHance following intravenous administration of MultiHance to individuals with end-stage renal disease that required dialysis. Dialysis was performed approximately 30 minutes after the administration of study drug. Comparison of the elimination half life during the dialysis period with the elimination half life of the off-dialysis period showed an approximately 35 fold decrease, with values of 1.21 hours as compared with 42.4 hours. Dialysate fluid collected during the dialysis accounted for a mean of 72% of the administered dose. These results show that gadobenate is dialyzable.

43,779-8 Safety and Pharmacokinetics on Patients with impaired Hepatic Function
Double-blind, parallel, randomized, placebo-controlled, single-center study. **[0.5M]**
IV injection over approx. 1 minute.
N = 16 12 males and 4 females,
11 received study drug and 5 received placebo.
0.1 mmol/kg = 11
Placebo = 5
Age from 30 – 61 years old, mean age = 47.8
Weight from 56 – 102 kg, Mean weight = 79
Blood and Urine
Gd levels determined.

Table. 8 PK summary of study 43,779-8

Study Number[c]	Route of Administration	Dose mmol/kg	Analyte	Vc (L/kg)	Vd_{area} (L/kg)	Vd (L/kg)	Vdss (L/kg)	$AUC_{0-\infty}$ (mg•hr/L)	t½ (hr)	CL (L/hr/kg)	CL_r (L/hr/kg)	Percent of Dose Eliminated via the Kidneys[h]
43,779-8	IV injection over approx. 1 minute.	0.5M MULTIHANCE 0.1 mmol/kg	Gadolinium in blood	ND	ND	0.33 (0.05)	0.28 (0.05)	138 (58)	2.06 (0.91)	0.128[d] (0.046)	0.106[d] (0.052)	80.2 (55.4 – 120)

This study was conducted to investigate the pharmacokinetics and safety of intravenously administered MultiHance in subjects with impaired hepatic function (Class B or C criteria of the modified Child-Pugh classification). The terminal elimination half life was 2.06 hr as compared with 1.81 hr in healthy male volunteers. Mean estimates of CL were 0.128 and 0.158 L/hr/kg and mean estimates of CL_r were 0.106 and 0.143 L/hr/kg for hepatically impaired and healthy male volunteers.

43,779-10 Safety and Pharmacokinetics on Healthy Pediatric Patients (2 - <16 years)
Open-label, single-center study. **[0.5M]**
IV injection over approx. 5 minutes.
N = 25 14 males and 11 females.
0.1 mmol/kg = 25
Age from 2 to <16 years old, Mean age = 9.8
Weight from 15.0 – 79.0, Mean weight = 37.9
Blood and Urine
Gd levels determined.

Table. 9 PK summary of study 43,779-10

Study Number[c]	Route of Administration	Dose mmol/kg	Analyte	Vc (L/kg)	Vd_{area} (L/kg)	Vd (L/kg)	Vdss (L/kg)	$AUC_{0-\infty}$ (mg•hr/L)	t½ (hr)	CL (L/hr/kg)	CL_r (L/hr/kg)	Percent of Dose Eliminated via the Kidneys[b]
43,779-10	IV injection over approx. 5 minutes.	0.5M MULTIHANCE 0.1 mmol/kg	Gadolinium in blood	0.170 (0.026)	ND	ND	ND	ND	1.51 (0.27)	0.199 (0.016)	ND	90.8 (5.1)

The study was conducted to investigate the pharmacokinetics and safety of intravenously administered MultiHance to pediatric subjects. The elimination half life was calculated as 1.51 hours in pediatric subjects, which compares with the value obtained at the same dose level in healthy adults of 1.21 hours. The mean estimate for CL was 0.20 L/hr/kg in pediatric subjects. Healthy male volunteers in the study had a comparable average value for CL of 0.16 L/hr/kg. The mean percent of the dose excreted in the urine of pediatric subjects was estimated as 91%, a value similar to the mean estimate of 86% observed in adult healthy male volunteers who received a same dose.

I. Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-357 / 21-358	Brand Name	MultiHance
OCPB Division (I, II, III)	3	Generic Name	Gadobenate Dimeglumine
Medical Division	DMIRDP	Drug Class	Contrast Agent
OCPB Reviewer	Hyun Kim	Indication(s)	See next page-comment section
OCPB Team Leader	David Lee	Dosage Form	529 mg
		Dosing Regimen	1
Date of Submission	27-Apr-2001	Route of Administration	Intravenous
Estimated Due Date of OCPB Review	24-Oct-2001	Sponsor	Bracco Diagnostics Inc.
PDUFA Due Date	27-Apr-2002	Priority Classification	S
Division Due Date	27-Feb-2002		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X			
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4		Only males
multiple dose:				
II. Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:	X			
pediatrics:	X	2		Phase 1=25 Phase 3=174
geriatrics:	X			1808 patients over 65 years old
renal impairment:	X	2		32 impaired 17 hemodialysis
hepatic impairment:	X	1		16 patients
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		9		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	***A 5-fold increase of Zn was found in the urine in the 24 hr period in renally impaired subject when compared to placebo. What is the safety significance of this finding? *Is MultiHance biodistribution similar to other products in use? *Reported blood level conc. never reached baseline. Sponsor should provide 0-T AUC and 0-Inf. AUC. Sponsor should also provide last time point in which the drug product was detectable. *Is 24 hr discontinuation of breast-feeding sufficiently safe?**	
Other comments or information not included above	***** indications: Intravenous use in adults as an adjunct to MRI of the CNS,**	
Primary reviewer Signature and Date		
~~Secondary reviewer~~ Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hyun Kwon Kim
2/22/02 04:03:12 PM
PHARMACOLOGIST

John P. Hunt
2/22/02 04:25:45 PM
BIOPHARMACEUTICS