CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020887

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 24 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-887 -- SUBMISSION DATE: 03/13/98

KIT FOR PREPARATION OF ^{99m}Tc TECHNETIUM APCITIDE
(ACUTECT®)

DIATECH, INC.
9 DELTA DRIVE
LONDONDERRY, NH 03053 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: AMENDMENT (SERIAL #AZ) CODE: 1P

SYNOPSIS/BACKGROUND

APPEARS THIS WAY
ON ORIGINAL

Amendment AZ was submitted to NDA 20-887 for Kit for Preparation of ^{99m}Tc Technetium Apcitide (Acutect®) by the sponsor on March 13, 1998. Acutect® is proposed as an intravenous agent for use with gamma scintigraphy in the detection and localization of acute venous thrombosis. The sponsor proposes that following intravenous administration of Acutect®, ^{99m}Tc technetium apcitide would bind "avidly and specifically" to the cell surface glycoprotein IIb/IIIa (GPIIb/IIIa) receptors of activated platelets in acute thrombi, via its argininyl-glycyl-aspartic acid component, and allow for scintigraphic imaging for the detection and localization of acute venous thrombosis. The package insert recommended dose of Acutect® is "**approximately 100 μg of peptide [bibapcitide] radiolabeled with approximately 20 mCi of ^{99m}Tc technetium**". In this amendment, the sponsor is responding to the Comments in the Agency's "**approvable**" letter dated February 20, 1998

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF INDIVIDUAL RESPONSES

1. Under item #7 the Agency requests the sponsor to evaluate "**the plasma and urine profiles**" and "**determine the pharmacokinetics of the metabolites [of Acutect®] in patients with renal impairment**".

APPEARS THIS WAY
ON ORIGINAL

The sponsor refers to the in vitro metabolic study that was submitted in the original NDA (Protocol M97-010) in which the metabolism of ^{3}H-labeled apcitide (P246), P1007 and P1008 in rat, rabbit and human liver and kidney slices was evaluated. In the current submission, the sponsor then states that "**the incubation of ^{3}H-labeled peptide components of technetium Tc 99m apcitide in human kidney slices produced multiple hydrophilic metabolites amounting to 23.9% of the applied radioactivity (i.e., peptide components)**". However, in the original NDA submission, the sponsor summarized the result of the metabolic study in question as follows:

"**Only marginal metabolism was observed for the human liver and kidney, rabbit liver and kidney and rat liver. The limited metabolism was mainly associated with the presence of a small polar component, possibly a specific metabolite, that appeared to elute just prior to P246. With the exception of the appearance of this small peak, the elution profiles in these samples were generally comparable with the reference solutions and media controls. However, a general increase in radioactivity levels above baseline observed for these tissue incubates was most likely associated with unresolved polar metabolites and/or degraded peptide species**" (original NDA: Volume 1.23 [page 000125]; [Appendix II: page 15 of this review: section 4.5]).

This summary of findings for the in vitro metabolic study does not appear to represent a conclusive statement of technetium ^{99m}Tc apcitide metabolism in human liver and kidney incubates. It also does not appear to be synonymous with the quantitative information, that "**the incubation of ^{3}H-labeled peptide components of technetium Tc 99m apcitide in human kidney slices produced multiple hydrophilic metabolites amounting to 23.9% of the applied radioactivity (i.e., peptide components)**", that is provided in this amendment.

In response to the Agency's comment, the sponsor intends to "**assess the feasibility of conducting a study to include radiation dosimetry and measurement of plasma and urinary metabolites [of Acutect®] in patients with moderate to severe renal dysfunction**".

The need for the requested pharmacokinetic and metabolic study of technetium ^{99m}Tc apcitide in patients with moderate renal impairment and in patients with severe renal impairment is further brought to the attention of the sponsor as covered under Overall Comment 1.

2. Under the Agency's **Comment #4** , it is requested that the "**effect of AcuTect on prolonging clinical bleeding time**" be studied. To this end, the sponsor proposes to conduct a clinical pharmacology study in **normal volunteers who have had no exposure to confounding medication.** For this study, the sponsor proposes to administer a dose of 100 μg of apcitide peptide and to measure bleeding time pre-dose and 10 min postdose ("**when peptide concentration is maximal**"). Using the results of this study, the effect of Acutect® on bleeding time would be determined.

3. In response to the Agency's **Comment #5** : that "**the effect of heparin, aspirin and coumadin on apcitide binding**" be studied, the sponsor states that "**the feasibility of conducting [such a study] in humans will be established**" based on pre-clinical study findings.

The sponsor is requested to also submit the protocols and findings of the proposed studies to the Division of Pharmaceutical Evaluation II for review as covered under Overall Comment 2.

OVERALL COMMENTS

1. On the issue of studying the kinetics of technetium ^{99m}Tc apcitide and its metabolites in patients with moderate renal impairment and in patients with severe renal impairment, it is stated that **"the feasibility of conducting a study to include radiation dosimetry and measurement of plasma and urinary metabolites in patients with moderate to severe renal dysfunction" will be assessed.** Since Acutect® is eliminated mainly by renal mechanisms, it is recommended that information on the pharmacokinetics and metabolism be obtained in these patient populations. The study protocol should be submitted to the Agency for review/input.

2. A study to examine **"the effect of Acutect® on prolonging clinical bleeding time"** in humans is being proposed and **"the feasibility"** of conduction a **"study in humans"** to assess the effect of heparin, aspirin and coumadin on apcitide binding is being examined . It is recommended that, prior to initiating these two studies, the study protocols should be submitted to the Division of Pharmaceutical Evaluation II for review. The basis of this request is to provide any input that may be necessary to design the study to yield optimal information on the pharmacodynamic aspects of Acutect® (Comment 4) and drug-drug interactions with Acutect® (Comment 5) related to these studies. Upon completing the studies, the study reports should also be submitted to the Division of Pharmaceutical Evaluation II for review.

3. The following comments relate to the **Clinical Pharmacology** portion of the proposed package insert. The pages cited are those of the propoesd package insert.

(a) Under **Pharmacokinetics**, the actual peptide **(bibapcitide)** used in the drug formulation needs to be specified. Thus, on **pages 3, 4 and 16,** needs to be retained. The term, could be replaced with the term,

(b) On **page 4**, the correct number of patients **(18 [14 men and 4 women)** should be stated. (Please note that in this study, **two of 20 subjects were normal volunteers and both were women**).

(c) On page 5, under **Special Populations**, "creatinine clearance" should be replaced with **"serum creatinine concentration"**.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION

Amendment AZ submitted to NDA 20-887 for Kit for Preparation of ^{99m}Tc Technetium Apcitide (Acutect®) by the sponsor on March 13, 1998 has been reviewed by the Division of Pharmaceutical Evaluation II of the office of Clinical Pharmacology and Biopharmaceutics. The issues raised in Overall Comments 1, 2 and 3 (page 3) need to be satisfactorily addressed by the sponsor.

Please convey this Recommendation and Overall Comments 1, 2 and 3 (page 3), as appropriate, to the sponsor.

Appendix I is retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

APPEARS THIS WAY
ON ORIGINAL

/S/ 06/24/98

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee, Ph.D. 06/18/98

FT Initialed by David Lee, Ph.D. /S/ 6/24/98

cc: NDA 20-887, HFD-160, HFD-160 (Ferre-Hockensmith), HFD-850 (Huang), HFD-870 (M. Chen, Hunt, Lee and Udo), CDR (Attn: Barbara Murphy).

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

TEAM LEADER'S MEMORANDUM

DATE: February 10, 1998

FROM: David J. Lee, Ph.D., Team Leader, Office of Clinical Pharmacology and Biopharmaceutics /S/ 2/12/98 (Signed-off)

TO: Dr. P. Love, Director, HFD-160

SUBJECT: ACUTECT™, NDA 20-887, Clinical Pharmacology and Biopharmaceutics Review

CC: HFD-160: A.E. Jones; V. Raczkowski; C. Ferre-Hockensmith
HFD-870: ML Chen; J. Hunt; D. Udo; D. Lee
NDA 20-887 Division File

APPEARS THIS WAY ON ORIGINAL

This memorandum has been constructed to provide the Team Leader's Clinical Pharmacology and Biopharmaceutics overview of NDA 20-887, AcuTect. This document will attempt to bring out the issues related to AcuTect pharmacokinetics. It should be noted that Dr. David Udo initiated the NDA review. However, due to a conflict Dr. Udo could not finish his review; At this time Dr. Udo's Clinical Pharmacology and Biopharmaceutics Review is in a draft form, and his review will be attached to this document as an appendix. In addition, the majority of the information presented in this document are from the Dr. Udo's draft review. The reader is encouraged to read Dr. Udo's draft review in conjunction with this document.

Previously, it should be noted that Dr. Udo shared his thoughts and presented his draft review to the reviewing medical division on November 21, 1997 (attendees: Drs. Love, Raczkowski, Jones, Zolman, Salako, Lee and Ferre-Hockensmith). In addition, the issues related to AcuTect review were discussed in detail.

APPEARS THIS WAY ON ORIGINAL

I. SYNOPSIS

NDA 20-887 for Kit for Preparation of ^{99m}Tc Technetium apcitide (Acutect™) was submitted by the applicant on August 20, 1997. The active ingredient of Acutect™ is ^{99m}Tc technetium apcitide. Acutect™ is proposed as an intravenous agent for use with gamma scintigraphy in the detection and localization of acute venous thrombosis. The applicant proposes that following intravenous administration of Acutect™, ^{99m}Tc technetium apcitide would bind "avidly and specifically" to the cell surface glycoprotein IIb/IIIa (GPIIb/IIIa) receptors of activated platelets in acute thrombi, via its argininyl-glycyl-aspartic acid component, and allow for scintigraphic imaging for the detection and localization of acute venous thrombosis. ^{99m}Tc technetium emits a gamma radiation with a mean energy of 140.5 keV. ^{99m}Tc technetium physical half-life is 6.02 hours. Apcitide (molecular weight [MW] = 1525.5 daltons) is a degradation product of bibapcitide (MW =3021.4 daltons).

In the Dosage and Administration section of the package insert, Acutect™ is recommended for administration as "a single dose of approximately 100 μg of peptide [bibapcitide] radiolabeled with approximately 20 mCi of ^{99m}Tc technetium". The applicant states that the selection of this dose was based on the results of a Phase II dose ranging study (Study 280-22) which showed that the optimal dose for the detection and localization of venous thrombosis was 20 mCi of ^{99m}Tc technetium and 80-100 μg of bibapcitide.

The applicant states (i) that during kit formulation and subsequent radiolabeling (i.e., heating the solution), bibapcitide is converted to smaller peptides (P1006, P1007, P1008 and apcitide), (ii) that apcitide binds ^{99m}Tc technetium to form the drug substance, ^{99m}Tc technetium apcitide, (iii) that during the preparation of the drug substance, bibapcitide and P1006 are completely converted to "apcitide, P1008 and P1007 in the approximate ratio of 20:15:65 , (iv) that these three peptides (and not bibapcitide and P1006) are present in the injectate and (v) that the presence of bibapcitide, P1006, P1007, P1008 and apcitide in the drug product and P1007, P1008 and apcitide in the injectate is predictable and reproducible.

In this NDA, the applicant submits three studies on the kinetics and metabolism of Acutect™, Protocols 280-10, 280-11 and M97-010. In Protocol 280-10, the kinetics of total radioactivity was evaluated in normal volunteers (n=10 [6 males and 4 females]) each receiving a single intravenous dose of Acutect™ containing 9.5-10.3 mCi of ^{99m}Tc technetium and 18-25 μg of bibapcitide.

In Protocol 280-11, the kinetics and plasma protein binding of total radioactivity, radioactive metabolites and the kinetics of the unlabeled peptide were determined in patients at risk of venous thrombosis [n= 18 (12 males and 6 females)] and two healthy male volunteers. "Patients at risk of venous thrombosis" was defined as patients who were "within 10 days of experiencing signs and symptoms of venous thrombosis or within 10 days of surgical procedures that puts them at a high risk of developing acute venous thrombosis". For this study, the radioactivity dose range and bibapcitide dose range for 19 of 20 subjects approximated the package insert recommended dose (20 mCi of ^{99m}Tc technetium and 100 μg of peptide). The to-be-marketed formulation, that was used in the well controlled clinical trials, was used in this study. In Protocol M97-010, the In vitro metabolism of 3H-labeled apcitide (P246), P1007 and P1008 in rat, rabbit and human liver and kidney was evaluated.

Total radioactivity exhibited biexponential kinetics (see below tables for pharmacokinetic parameters). The mean ± SD biliary excretion was 10.1 ± 2.5 %ID. The mean ± SD plasma protein binding determined in patients was 75.8 ± 13.4 %. It appeared that the kidney could be a major site of both metabolism and elimination. The highest mean ± SD total radioactivity for any single organ was 15.3 ±5.3%ID observed in the urinary bladder in normal volunteers at 10 minute postdose.

From a clinical pharmacology and biopharmaceutics perspective, it is felt that this application should be considered "approvable", pending that the applicant provides adequate responses to the labeling and review comments made in this document.

II. CHEMISTRY

United States Adopted Name (USAN): Bibapcitide

Chemical Name: 13,13'-[oxybis[methylene(2,5-dioxo-1,3-pyrrolidinediyl)]bis[N-(mercaptoacetly)-D-tyrosyl-S-(3-aminopropyl)-L-cysteinylglycyl-L-α-aspartyl-L-cysteinlyglycylglycyl-S-[(acetylamino)methyl]-L-cysteinylglycyl-S-[(acetylamino)methyl]-L-cysteinylglycylglycyl-L-cysteinamide], cyclic (1-5), (1'-5')-bis(sulfide)

Code name: Peptide P280
Molecular Formula: $C_{112}H_{162}N_{36}O_{43}S_{10}$
Molecular Weight: 3021.4 (anhydrous)
Stereochemistry: All chiral amino acids are of the L configuration except D-Tyrosine

Appearance:	White powder
Solubility:	Trifluoroacetate salt is very slightly soluble in water, methanol, ethanol, and acetonitrile. The bibapcitide trifluoroacetate solid must first be wetted with an organic solvent such as ethanol, acetonitrile, or propylene glycol to produce a fine suspension, followed by the addition of aqueous solution to dissolve the solid.
Solution pH:	pH 23.8 in solution containing 10% propylene glycol in water v/v.
Melting point:	Bibapcitide trifluoroacetate decomposes above 248°C.

III. FORMULATION

Component	Quantity per vial (1 ml)
Bibapcitide Trifluoroacetate	100 μg
Sodium α-D-Glucoheptonate Dihydrate	75 mg
Tin Chloride Dihydrate	89 μg
Hydrochloric Acid	
Sodium Hydroxide	

IV. INDICATIONS AND USAGE

The applicant stated in the package insert that:

AcuTect is indicated for scintigraphic imaging of acute venous thrombosis.

V. DOSAGE AND ADMINISTRATION

The applicant stated in the package insert that:

Technetium Tc 99m apcitide is administered in a single dose of approximately 100 μg of peptide radiolabeled with approximately 20 mCi of technetium-99m. The contents of one reconstituted vial should be administered to one patient. Imaging should be performed 10 to 60 minutes following administration of the agent.

Dose adjustment has not been established in patients with renal insufficiency, or in pediatric or geriatric patients.

VI. PHARMACOKINETICS OF ACUTECT

APPEARS THIS WAY
ON ORIGINAL

A. SAMPLE ANALYSIS

For pharmacokinetic analysis of total radioactivity, blood and urine samples were analyzed by counting in a gamma scintillation counter and the unlabeled peptide was quantified using the . Metabolism was assessed and plasma protein binding was determined by the centrifuge-assisted ultrafiltration method for the 30 min plasma sample.

B. RADIOACTIVITY PHARMACOKINETICS

Total radioactivity exhibited biexponential kinetics in studies. In normal volunteers (dose: approximately 10 mCi), the mean ± SD pharmacokinetic parameters were as follows:

Parameter	Overall Value (n=10)	Male (n=6)	Female (n=4)
$t_{1/2}$ h	2.53 ± 2.76	3.07 ± 3.50	1.73 ± 0.71
Cl_{total} ml/min/kg	1.53 ± 0.27	1.49 ± 0.32	1.59 ± 0.23
V_c L/kg	0.09 ± 0.03	0.09 ± 0.02	0.14 ± 0.03
V_{ss} L/kg	0.25 ± 0.15	0.25 ± 0.17	0.26 ± 0.13
$V_{d\beta}$ L/kg	0.29 ± 0.22	0.33 ± 0.29	0.23 ± 0.07

In 18 patients at risk of venous thrombosis and two healthy volunteers (dose: approximately 20 mCi), the mean ± SD pharmacokinetic parameters were as follows:

Parameter	Overall Value (n=20)	Male (n=14)	Female (n=6)
$t_{1/2}$ h	2.0 ± 0.50	2.0 ± 0.55	2.1 ± 0.79
Cl_{total} ml/min/kg	1.9 ± 0.70	1.9 ± 0.68	2.1 ± 0.79
V_{ss} L/kg	0.16 ± 0.06	0.15 ± 0.04	0.17 ± 0.13
$V_{d\beta}$ L/kg	0.33 ± 0.12	0.31 ± 0.08	0.39 ± 0.18

C. URINE SAMPLES

The mean ± SD amounts of total radioactivity ultimately eliminated in urine was 79.5 + 5.8%ID (n = 10) for normal volunteers (78.5 ± 7.4%ID [n = 6] for males and 81.0 ± 2.2%ID [n = 4] for females) and 56.7 + 13.4%ID (n = 9) for patients. These data suggest (I) that urinary excretion is the major route of Acutect™ elimination in healthy individuals and in patients at risk of venous thrombosis and (ii) that in healthy individuals, renal elimination of Acutect™ is not affected by gender. Only two female patients were evaluated for urinary excretion of radioactivity; therefore, a gender analysis in this patient population was not feasible. Based on the SD values, the RSD values were 7.3% in normal volunteers (9.4% for males and 2.7% for females) and 13.4% in patients at risk of venous thrombosis. These results suggest low variability in cumulative renal elimination of Acutect™ in normal volunteers and in patients at risk of venous thrombosis.

D. BILIARY EXCRETION

The mean ± SD biliary radioactivity excretion was 10.1 ± 2.5%ID (n = 10) in normal volunteers. Biliary excretion could not be estimated for patients as only the gallbladder (and not the gastrointestinal tract) was evaluated as a region of interest.

In normal volunteers (Protocol 280-10), biliary excretion of radioactivity was estimated as the total amount of radioactivity in the gastrointestinal tract and gallbladder as determined by scintigraphic imaging. The overall mean ± SD biliary excretion at 22-24 h post dose was 10.1 ± 2.5%ID ([n = 10], 9.6 ± 3.2%ID [n = 6] for males and 10.7 ± 2.5%ID [n = 4] for females). The SD values represent RSD values ranging from 23% to 33 % suggesting moderate variability of biliary excretion of Acutect™ in healthy individuals. These results suggest that in healthy individuals, biliary excretion of Acutect™ is not affected by gender. In patients at risk of venous thrombosis, the gallbladder was evaluated as an ROI, but the gastrointestinal tract was not. Subsequently, the total amount of radioactivity excreted in the bile could not be determined.

E. PROTEIN BINDING INFORMATION

In vivo plasma protein binding of total radioactivity in patients was determined by the centrifuge-assisted ultrafiltration method using the 30 min plasma sample (Protocol 280-11). The mean ± SD plasma protein binding was 75.8 ± 13.4% ([n = 16], 75.5 ± 15.4% [n = 11] for males and 76.3 ± 8.7% [n = 5] for females).

F. METABOLISM OF RADIOACTIVE PEPTIDE:

The submission contained the information regarding the presence of radioactive metabolites in the blood or urine of subjects receiving Acutect™; this was assessed by a reverse phase with fraction collection (Protocol 280-11). It should be noted that however, the information presented by the applicant is not conclusive due to inconsistency in the appearance of the metabolites in plasma and urine samples. The applicant presented the following information. Two unidentified, radioactive metabolites, both more polar than the parent drug were observed in urine. The more polar of the two metabolites was estimated at < 10% of total radioactivity while the other metabolite was estimated at < 30% of total radioactivity. The more polar metabolite was also detected in plasma. Literature information indicates that protein drugs with MW < 30,000 daltons tend to be filtered in the glomeruli of the kidneys, taken up by the cells of the proximal tubules of the kidney and metabolized and that

very little amounts of such drugs are eliminated unchanged in the urine. This suggests (I) that the kidney may be the major site of metabolism of ^{99m}Tc technetium apcitide as well as the site of its eventual elimination from the body and (ii) that the radioactivity detected in the urine following Acutect™ administration may represent predominantly ^{99m}Tc technetium apcitide metabolites. The in vitro study of the metabolism of 3H-labeled apcitide, P1007 and P1008 in rat rabbit and human slices did not yield any further insight into the metabolism of these peptides.

G. Ex Vivo PLATELET AGGREGATION STUDY

In Protocol 280-11, the applicant conducted an ex vivo platelet aggregation study. Approximately 10 ml blood samples were obtained before and within 3-6 minutes following the administration of Tc99m Apcitide. To these blood samples ADP (adenosine 5-diphosphate) was added to induce platelet aggregation. Platelet aggregation was measured by turbidometry. Five subjects were enrolled into the study.

The results indicated that of these, technically successful aggregation measurements were obtained from one subject; technical difficulties included instrument malfunction, small clot in pre-injection sample, and pre-injection value out of normal range. In the one successful measurement, the difference between the extent of aggregation of the pre- and post-injection samples was within the limits of normal variation. The applicant concluded that the administration of the recommended clinical dose of Tc99m Apcitide injection does not result in inhibition of platelet aggregation.

This reviewer felt that the applicant's conclusion can not be supported by the data obtained from the study due to the limited number of subjects

The applicant does not have substantial data to support the conclusion due to the lack of data obtained from this study; as stated above, one successful measurement was produced from the study. Therefore, it is felt that the data do not support the result that Tc99m Apcitide injection does not result in inhibition of platelet aggregation.

H. SPECIAL POPULATIONS:

1. Patients with Impaired Renal Function:

No studies were conducted to evaluate the disposition of Acutect™ in patients with impaired function. In Protocol 280-11, the serum creatinine of one patient (Patient 0004000007) was (normal range for the study: < 1.5 mg/dL). The percentage of the injected radioactivity eliminated in urine in 24 hours by this patient (59.9%) was within the range eliminated in the same time interval by patients with serum creatinine less than 1.5 mg/dL In the proposed package insert, under Dosage and Administration, it is stated that dosage adjustment has not been established in patients with renal insufficiency. Literature information indicates that protein drugs of the molecular size of apcitide are significantly metabolized in the kidney. Therefore, it appears that for ^{99m}Tc apcitide, the kidney could be a major organ of metabolism as well as the organ of eventual eliminations. Due to the paramount role that the kidneys might play in the elimination of this drug, a study in renally impaired subjects may be considered.

2. **Pediatric Patients:**

Studies have not been conducted to assess the disposition of Acutect™ in pediatric patients. In the proposed package insert, (I) under Pediatric Use, it is stated that "safety and effectiveness [of Acutect™ in pediatric patients have not been established" and (ii) under Dosage and Administration, it is stated that dosage adjustment has not been established in pediatric patients.

APPEARS THIS WAY
ON ORIGINAL

I. DRUG-DRUG INTERACTIONS:

No pharmacokinetic studies were conducted to assess possible interactions of Acutect™ with any concomitantly administered drug. In the proposed package insert, under Drug Interactions, it is stated that "drug interactions were not noted in clinical studies in which technetium Tc 99m apcitide was administered to patients receiving concomitant medications". In the NDA, it is stated that the "concomitant medications" included the antithrombotic agents, warfarin (99% plasma protein bound), heparin (extensively plasma protein bound), acetylsalicylic acid and enoxaparin (Protocol 280-11). No quantitative data from the "clinical studies" were provided to support this statement.

APPEARS THIS WAY
ON ORIGINAL

VII. PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) RELATIONS:

The optimal imaging time stated in the package insert is 10-60 min post dose. In patients (Protocol 280-11), this time interval corresponds to ≥62.5 ± 15.3%ID in plasma at imaging time. The applicant states that some adverse events and some statistically significantly abnormal clinical laboratory and hematological parameters were noted in clinical studies using the proposed dose stated in the package insert of Acutect™. The times of observation of these events relative to Acutect™ administration were not stated. Therefore, an attempt to relate these events to the pharmacokinetics of the drug is not feasible. The applicant also states that in clinical studies, there were no drug-drug interactions of ^{99m}Tc technetium apcitide with concomitantly administered drugs such as warfarin, coumadin and acetylsalicylic acid. No quantitative data were provided to support this statement.

APPEARS THIS WAY
ON ORIGINAL

VIII. RADIOACTIVITY CONTENTS OF REGIONS OF INTEREST (ROI)

Only small fractions of radioactivity were present in any single internal organ at any time following drug administration. The highest mean ± SD total radioactivity for any single internal organ was 15.3 ± 5.3%ID (n = 10) observed in the urinary bladder in normal volunteers at 10 min post dose.

For normal volunteers (Protocol 280-10) and in patients at risk of venous thrombosis, (Protocol 280-11), the mean ± SD values for the first imaging time (10 min post dose), 4 h post dose and/or last imaging time (22-24 h) post dose are summarized below.

APPEARS THIS WAY
ON ORIGINAL

Normal Volunteers (Mean ± S.D. % Injected Dose (ID)) (see appendix for Dr. Udo's review)

	10 minute			4 hour			22-24 hour		
	Overall n=10	Male n=6	Female n=4	Overall n=10	Male n=6	Female n=4	Overall n=10	Male n=6	Female n=4
Whole Body	84.7±5.4	84.9±6.1	84.5±5.3	23.1±3.9	23.2±4.4	23.0±3.8	-	-	-
Lung	4.4±0.6	4.6±0.6	4.1±0.7	0.8±0.2	0.8±0.2	0.7±0.3	-	-	-
Heart	3.5±0.8	3.3±0.6	3.8±0.9	0.5±0.1	0.6±0.1	0.5±0.2	-	-	-
Spleen	1.5±0.5	1.6±0.4	1.5±0.7	0.4±0.2	0.4±0.2	0.5±0.2	-	-	-
Breast	-	-	4.4±1.2	-	-	1.0±0.8	-	-	-
Liver	10.1±1.2	9.8±1.0	10.6±1.4	-	-	-	1.8±0.5	1.8±0.3	2.0±0.7
Kidneys	7.3±1.8	6.2±0.9	8.9±1.6	1.9±0.5	1.8±0.2	2.1±0.8	-	-	-
Urinary bladder	15.3±5.4	15.6±6.6	15.5±5.3	-	-	-	-	-	-
Brain	-	-	-	-	-	-	-	-	-
Gall-bladder	-	-	-	-	-	-	-	-	-

Patients (Mean ± S.D. % Injected Dose (ID)) (see appendix for Dr. Udo's review)

	10 minute			22-24 hour		
	Overall n=20	Male n=14	Female n=6	Overall n=20	Male n=14	Female n=6
Whole Body	100	100	100	16.18±4.93	16.2±5.09	16.16±5.01
Lung	8.42±1.68	8.86±1.63	7.41±1.42	0.67±0.3	0.77±0.29	0.42±0.10
Heart	2.76±0.60	2.82±1.83	2.62±0.34	0.2±0.08	0.22±0.08	0.6±0.05
Spleen	1.02±0.35	0.98±0.36	1.13±0.36	0.48±0.49	0.39±0.38	0.68±0.69
Breast	-	-	-	-	-	-
Liver	6.56±1.61	6.11±1.17	7.63±2.09	1.17±0.54	1.07±0.51	1.39±0.59
Kidneys	5.95±2.06	5.6±1.46	6.75±3.09	2.19±1.3	1.86±1.10	2.97±1.49
Urinary bladder	11.6±4.25	10.97±4.0	13.2±4.82	0.52±0.6	0.57±0.7	0.41±0.27
Brain	1.17±0.27	1.21±0.29	1.08±0.20	0.13±0.05	0.14±0.05	0.09±0.03
Gall-bladder	0.55±0.25	0.46±0.37	0.44±0.77	0.19±0.26	0.16±0.18	0.25±0.41

A. Abdomen:

For normal volunteers, most of the SDs for the ROIs represent RSD suggesting that in general, following intravenous doses of Acutect™, inter individual variability in amounts of radioactivity in the ROIs is low to moderate. In patients, RSD values in most cases also suggesting low to moderate variability in the related amounts of radioactivity. However, higher variability was observed in some cases

The high inter individual variability in the amounts of radioactivity in the gallbladder of these patients suggests high individual inter individual variability of biliary excretion of radioactivity.

In patients, the overall mean ± SD was 15.38 ± 3.39%ID ([n = 20], 15.67 ± 3.67%ID [n = 14] for mares and 14.71 ± 8.82%ID [n = 6] for females) at 10 min post dose and declined to 5.85 ± 12.72 %ID ([n = 20], 5.74 ± 2.82%ID [n = 14] for males and 6.11 ± 2.70 %ID [n = 6] for females) at 24 h post dose. In normal volunteers, the abdomen was not evaluated as a single region of interest.

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IX. DOSIMETRY

Radiation absorbed dose: In the proposed package insert, under Radiation Dosimetry, the applicant provides a table of mean estimated absorbed radiation dose for specific organs of to an average (70 kg) adult from an intravenous injection of Acutect™. The values were based on urinary bladder emptying at 4.8 h post dose. The limits of organ absorbed radiation from administered radionuclide doses "for certain research uses" are specified as follows: for "whole body, active blood-forming organs lens of the eye and gonads": ≤ 3 rems from a "single dose" and 5 rem for "annual and total dose commitment"; for other organs": ≤ 5 rem from a "single dose" and 15 rem for "annual and total dose commitment" (21 CFR 361.1)(b)(3). The absorbed radiation dose stated for each organ in the proposed package insert is within the limits specified in the CFR for a single radionuclide dose administration. (*: As per Dr. Udo's draft review)

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X. LABELING COMMENTS

The Labeling Comments will be covered under a separate review. The Office of Clinical Pharmacology and Biopharmaceutics has proposed a CLINICAL PHARMACOLOGY label that presents information systematically. The proposed labeling should be conveyed to the applicant as appropriate.

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XI. NDA REVIEW COMMENTS

1. Pharmacokinetics of Tc99m-Apcitide

The NDA package contained the total radioactivity pharmacokinetic data. The radioactivity counting procedure that was utilized is a "non-discriminating" analysis, i.e., the scintillation counting method follows the "radioactive nuclei containing moieties" and counts the "total" radioactivity. Therefore, it was concluded that the radioactivity data represented the information on Tc99m-attached moieties, and did not provide discrete information regarding Tc99m-Apcitide moiety alone.

However, the applicant did submit the plasma and urine sample profiles. The applicant did not analyze this information quantitatively. It is felt that this information can be used to provide characteristics of Tc99m-Apcitide. Therefore, the applicant should reanalyze the plasma and urine profiles to obtain pharmacokinetics of Tc99m apcitide. The results of apcitide plasma and urine reanalyses should be submitted to the agency for a review.

2. Pharmacokinetics of Metabolites

As mentioned above (Comment #1), it is felt that metabolite formation information, e.g., appearance rates of Metabolites A and B, may be obtained from the plasma and urine sample profiles. Therefore, the applicant should reanalyze the plasma and urine profiles to obtain pharmacokinetics of Tc99m apcitide metabolites. The results of apcitide plasma and urine reanalyses should be submitted to the agency for a review.

3. Limited renal function impairment

Regarding elderly patients enrolled in Protocol 280-11, although the applicant described these patients as patients with "mild" renal dysfunction, it is not clear whether these elderly patients actually suffer from the limited renal dysfunction. It was felt that the serum creatinine values reported for these patients may be in the normal range for this age group
Therefore, it is considered that no conclusive pharmacokinetic information was submitted on the disposition of AcuTect I renally impaired subjects.

It should be noted that the applicant stated in the 280-11 study report that:

> "...The total clearance seemed to decline slowly with age. It probably reflected the physiologic change with aging. There was a trend that total clearance was reduced with elevated creatinine levels. The renal clearance plots were difficult for observing a trend because fewer data points were available. Same as any drug that renal elimination played a significant role in clearance, *technetium-99m P280 should be used with caution in patients with significant renal functional impairment.*"

In addition to the applicant's concern stated above, since it appears that the kidney may be the major site of metabolism and eventual elimination of AcuTect, it is recommended that pharmacokinetic data be obtained in the renal patient population.

4. Dr. Udo's General Comments

The reader is encouraged to read Dr. Udo's Labeling Comments (#1 and 2) and General Comments (#2, 3, 4, 5, and 6) under his draft review, pages 19 and 20, respectively, in conjunction with this document.

XII. COMMENTS TO THE APPLICANT

Above NDA REVIEW COMMENTS (#1,2, 3, and 4) and the Labeling Comments should be conveyed to the applicant as appropriate.

XIII. RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of NDA 20-887, for Tc99m technetium apcitide (AcuTect), that was submitted by the applicant on August 20, 1997, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II; HFD-870).

From a clinical pharmacology and biopharmaceutics perspective, it is felt that this application should be given an "approvable" status, pending that the applicant provides adequate responses to the labeling and review comments made in this document.

The NDA review and Labeling Comments (to be covered under a separate review) should be conveyed to the applicant as appropriate.

/S/ 2/19/98

David J. Lee, Ph.D.
Pharmacokineticist, Team Leader
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

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Concurrence:

/S/ 2/20/98

John Hunt
Deputy Director
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

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ON ORIGINAL

Clinical Pharmacology/Biopharmaceutics Briefing: Attendees: Mei-Ling Chen, John Hunt, John Lazor, Mehul Mehta, Joseph Zolman, David Lee, David Udo, Young-Moon Choi, Alfredo Sancho, Shiew-Mei Huang. 2/18/98 9:00 am.

CC:		
	HFD-160	NDA 20-737; DIV FILE; /CSO/FERRE (1X); /OCPB/DLEE; /OCPB/DUDO
	HFD-870	/OCPB/JHUNT (1x); /OCPB/MLCHEN (1X)
	HFD-850	/OCPB/SHUANG
	CDR	Attn: Barbara Murphy

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APPENDIX I

Dr. David Udo's draft Clinical Pharmacology and Biopharmaceutics Review.

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-887-- SUBMISSION DATE: 08/20/97

KIT FOR PREPARATION OF ^{99m}Tc TECHNETIUM APCITIDE
(ACUTECT®)

DIATECH, INC.
9 DELTA DRIVE
LONDONDERRY, NH 03053 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: ORIGINAL SUBMISSION CODE: 1P

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VIII.	Proposed Annotated Draft Package Insert	///

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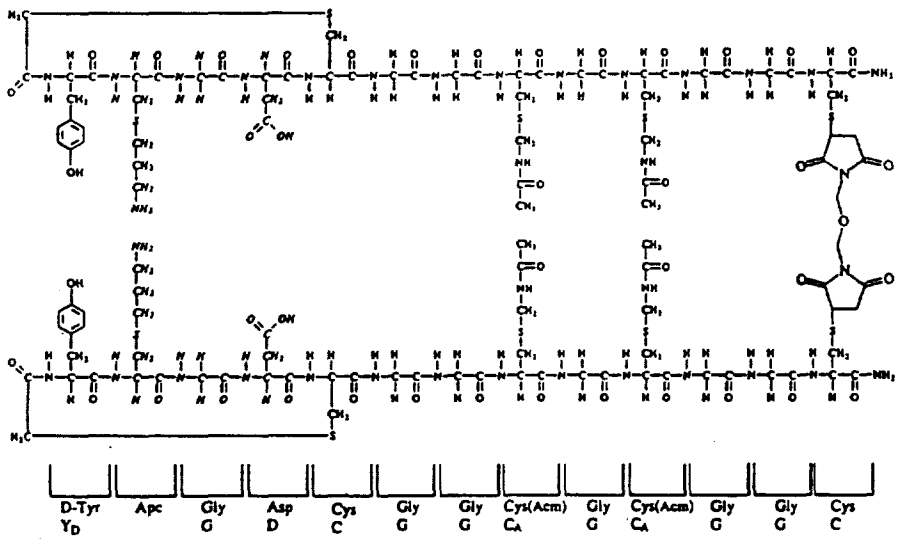
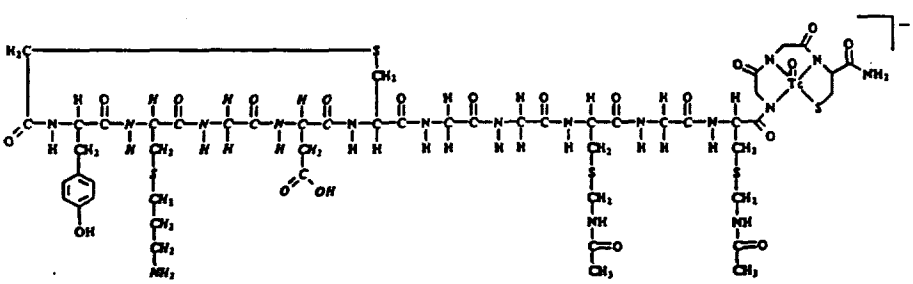
SYNOPSIS/BACKGROUND

NDA 20-887 for Kit for Preparation of ^{99m}Tc Technetium Apcitide (Acutect®) was submitted by the sponsor on August 20, 1997. Acutect® is proposed as an intravenous agent for use with gamma scintigraphy in the detection and localization of acute venous thrombosis. The sponsor proposes that following intravenous administration of Acutect®, ^{99m}Tc technetium apcitide would bind "avidly and specifically" to the cell surface glycoprotein IIb/IIIa (GPIIb/IIIa) receptors of activated platelets in acute thrombi, via its argininyl-glycyl-aspartic acid component, and allow for scintigraphic imaging for the detection and localization of acute venous thrombosis.

In the **Dosage and Administration** section of the package insert, Acutect® is recommended for administration as **"a single dose of approximately 100 μg of peptide [bibapcitide] radiolabeled with approximately 20 mCi of ^{99m}Tc technetium"**. The sponsor states that the selection of this dose was based on the results of a Phase II dose ranging study (Study 280-22) which showed that the optimal dose for the detection and localization of venous thrombosis was 20 mCi of ^{99m}Tc technetium and of bibapcitide. The structures of bibapcitide and ^{99m}Tc technetium apcitide are presented below.



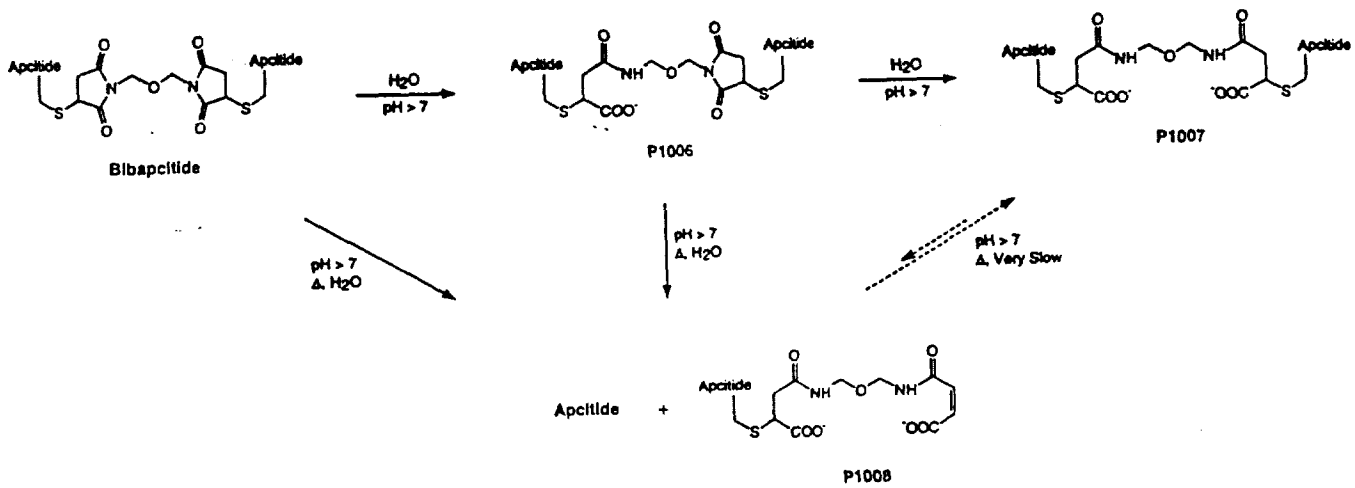
Bibapcitide



Technetium Tc 99m Apcitide

The active ingredient of Acutect® is ^{99m}Tc technetium apcitide. ^{99m}Tc technetium emits a gamma radiation with a mean energy of 140.5 keV. Its physical half-life is 6.02 h. Apcitide (molecular weight [MW]=1525.5 daltons) is a degradation product of bibapcitide (MW=3021.4 daltons). A schematic of the production of apcitide from bibapcitide is presented below.

Figure 2.D.1-1. Chemistry of Bibapcitide and Related Substances



The sponsor states (i) that during kit formulation and subsequent radiolabeling, bibapcitide is converted to smaller peptides (P1006, P1007, P1008 and apcitide), (ii) that apcitide binds ^{99m}Tc technetium to form the drug substance, ^{99m}Tc technetium apcitide, (iii) that during the preparation of the drug substance, bibapcitide and P1006 are completely converted to "apcitide, P1008 and P1007 in the approximate ratio of 20:15:65 , (iv) that these three peptides (and not bibapcitide and P1006) are present in the injectate and (v) that the presence of bipapcitide, P1006, P1007, P1008 and apcitide in the drug product and P1007, P1008 and apcitide in the injectate is "predictable and reproducible".

The HFD-160 chemistry review team has raised questions about the relative quantities of P1007, P1008 and apcitide in the injectate. Regardless of how this issue is resolved, the course of the pharmacokinetics review will not be significantly altered as the kinetics of apcitide (which is present in the injectate as ^{99m}Tc technetium apcitide in the injectate) and P1007 have been evaluated in the pharmacokinetic studies.

In this NDA, the sponsor submits three studies on the kinetics and metabolism of Acutect®, Protocols 280-10, 289-11 and M97-010. In Protocol 280-10, the kinetics of total radioactivity was evaluated in normal volunteers (n=10 [6 males and 6 females]) each receiving a single intravenous dose of Acutect® containing of ^{99m}Tc technetium and of

bipapcitide.

In Protocol 280-11, the kinetics and plasma protein binding of total radioactivity, radioactive metabolites and the kinetics of the unlabeled peptide were determined in patients at risk of venous thrombosis (n=18 [12 males and 14 females) and two healthy male volunteers. **"Patients at risk of venous thrombosis" was defines as patients who were "within 10 days of experiencing signs and symptoms of venous thrombosis or within 10 days of surgical procedures that puts them at a high risk of developing acute venous thrombosis".** For this study, **the radioactivity dose range , and bibapcitide dose range for 19 of 20 subjects approximated the package insert recommended dose (20 mCi of ^{99m}Tc technetium and 100 μg of peptide).** The radioactivity dose for one subject was 13.90 mCi. The bibapcitide dose for one subject was 65.0 μg. The to-be-marketed formulation, that was used in the well controlled clinical trials, was used in this study. In Protocol M97-010, the in vitro metabolism of ^{3}H-labeled apcitide (P246), P1007 and P1008 in rat, rabbit and human liver and kidney was evaluated.

For pharmacokinetic analysis of total radioactivity, blood and urine samples were analyzed by counting in a gamma scintillation counter and the unlabelled peptide was quantified using the . Metabolism was assessed and plasma protein binding was determined by the for the 30 min plasma sample.

Total radioactivity exhibited biexponential kinetics in studies. **In normal volunteers,** the mean±SD pharmacokinetic parameters were as follows: $t_{1/2}$: 2.53±2.76 h (n=10), Cl_T: 1.53±0.27 mL/min/kg (n=10), V_c: 0.09±0.03 L/kg (n=9), V_{ss}: 0.25±0.15 L/kg (n=10) and $V_{d\beta}$: 0.29±0.22 L/kg (n=10). **In 18 patients at risk of venous thrombosis and two healthy volunteers,** the mean±SD pharmacokinetic parameters were as follows: $t_{1/2}$: 2.0±0.50 h (n=20), Cl_T: 1.9±0.70 mL/min/kg (n=20), V_{ss}: 0.16±0.06 L/kg (n=20) and $V_{d\beta}$: 0.33±0.12 L/kg (n=20). The mean±SD amounts of total radioactivity ultimately eliminated in urine was 79.5±5.8%ID (n-10) for normal volunteers and 56.7±13.4%ID (n=9) for patients. The mean±SD biliary excretion was 10.1±2.5%ID (n=10) in normal volunteers. Biliary excretion could not be estimated for patients as only the gallbladder (and not the gastrointestinal tract) was evaluated as a region of interest. The mean±SD plasma protein binding determined in patients was 75.8±13.4% (n=16). In general, in normal volunteers and patients receiving intravenous doses of Acutect®, inter individual variability in the kinetics of total radioactivity was low to moderate. For unlabeled peptides evaluated in patients, plots of plasma concentration versus time were rather erratic, and would not yield useful pharmacokinetic parameters. The erratic nature of the curves appears to suggest entero-hepatic cycling of the unlabeled peptide. A significant amount of the unlabelled peptide was eliminated in urine. In the in vivo metaboism study in patients, two unidentified, radioactive metabolites were observed. The in vitro metabolism study yielded no additional insight into the metabolism of the radiolabeled or unlabelled peptide as no more than two unidentified metabolites were observed in any case. As covered under item # 5 (page 16), the kidney could be a major site of both metabolism and eventual elimination from the body for ^{99m}Tc technetium apcitide.

As expected of protein drugs with MW <30,000 dalton, only small fractions of radioactivity were present in any single internal organ at any time following drug administration as covered under item #1(d) (pages 12-14). The highest mean±SD total radioactivity for any single internal organ was 15.3±5.3%ID (n-10) observed in the urinary bladder in normal volunteers at 10 min postdose.

The findings of the pharmacokinetic studies in normal volunteers and patients (Protocols 280-10 and 2809-11) suggest that following intravenous injection of Acutect®, the kinetics, plasma protein binding and tissue distribution of total radioactivity are not affected by age or gender.

The optimal imaging time stated in the package insert is 10-60 min postdose. In patients (Protocol 280-11), this time interval corresponds to ≤62.5±15.3%ID in plasma at imaging time. The sponsor states that some adverse events and some statistically significantly abnormal clinical laboratory and hematological parameters were noted in clinical studies using the proposed dose stated in the package insert of Acutect®. The times of observation of these events relative to Acutect® administration were not stated. Therefore, an attempt to relate these events to the pharmacokinetics of the drug is not feasible. The sponsor also states that in clinical studies, there were no drug-drug interactions of ^{99m}Tc technetium apcitide with concomitantly administered drugs such as warfarin, coumadin and acetylsalicylic acid. No quantitative data were provided to support this statement.

A consideration of the paramount role of the kidneys in the elimination of ^{99m}Tc technetium apcitide in the wording of the statement of precaution, warning or contraindication of the drug product as they relate to patients with impaired renal function has been suggested to the reviewing medical officer as covered under Overall Comment 1.

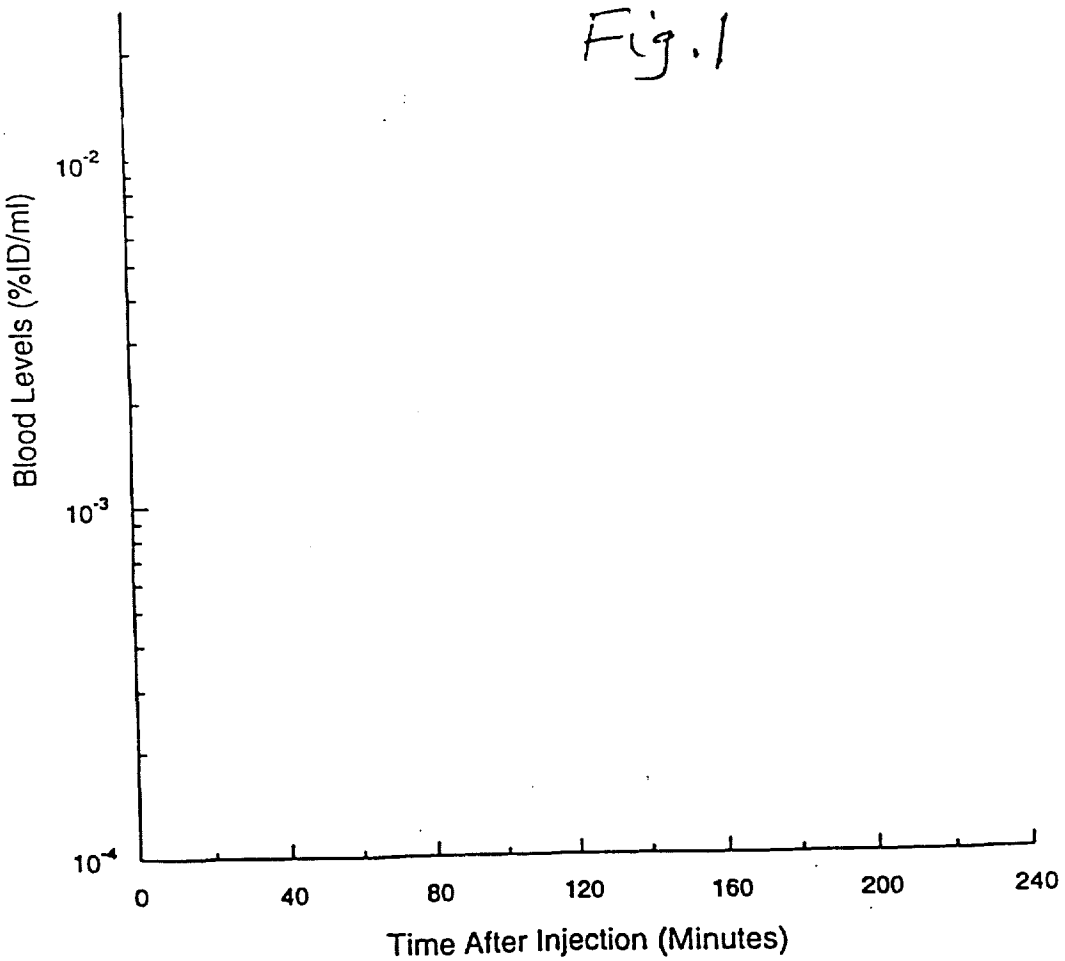
Overall, it is considered that adequate clinical pharmacokinetic information has been provided to support the approval of the NDA.

II. SUMMARY OF INFORMATION ON BIOAVAILABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, METABOLISM, DRUG-DRUG INTERACTIONS, ETC.

1. PHARMACOKINETICS:

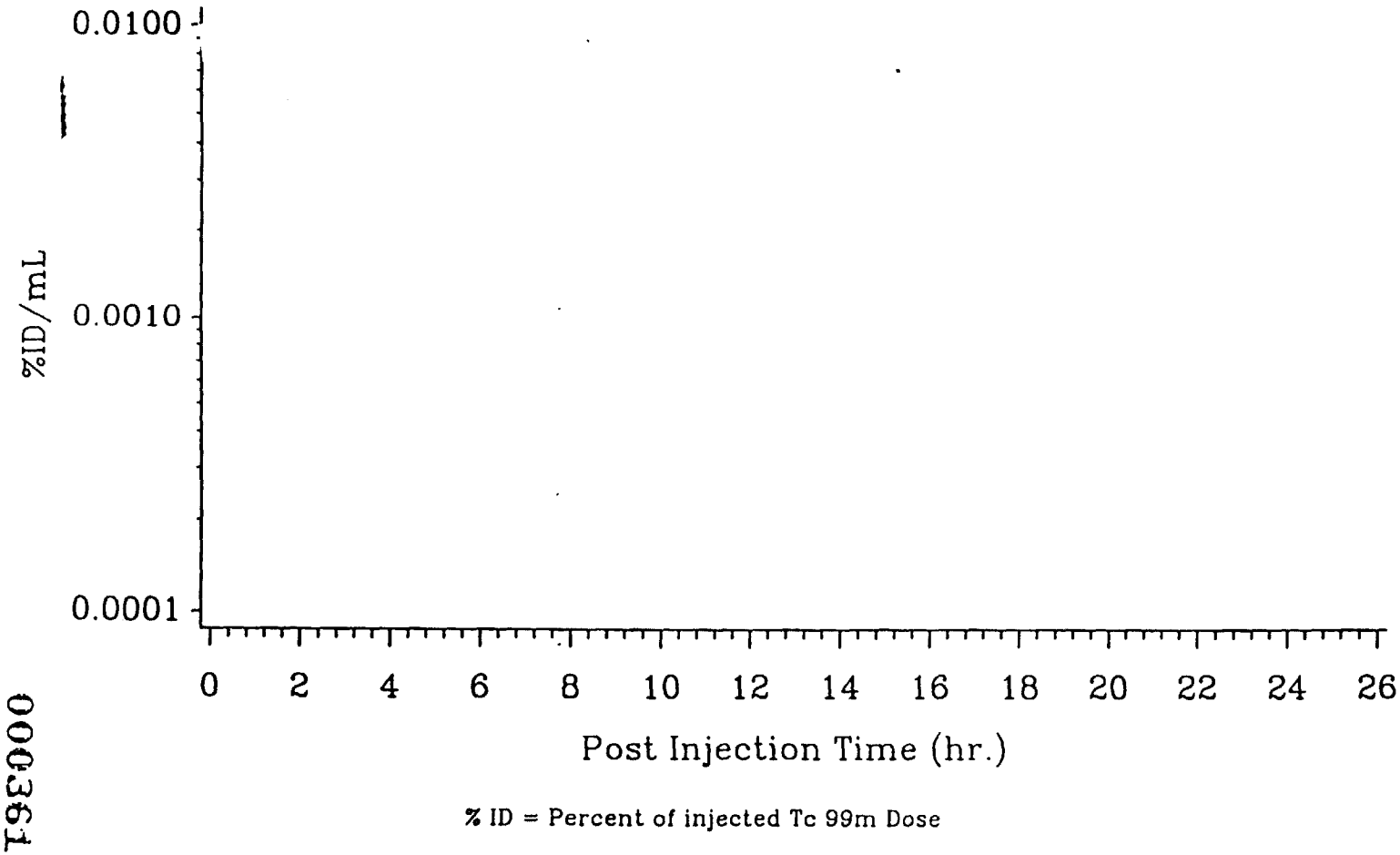
(a) **Pharmacokinetics from Blood Data**: The kinetics of ^{99m}Tc was evaluated in healthy volunteers ([n=10], 6 males and 4 females) each receiving a single intravenous injection of Acutect® containing 9.5-10.3 mCi of ^{99m}Tc technetium and 18-25 μg of bipapcitide (Protocol 280-10) and in 18 patients (12 males and 6 females) at risk of venous thrombosis and two healthy male volunteers, each receiving a single intravenous injection of Acutect® containing 13.9-21.2 mCi of ^{99m}Tc technetium and 70-90 μg of bipapcitide (Protocol 280-11). In Protocol 280-11 where the kinetics was more satisfactorily characterized, total radioactivity exhibited biexponential kinetics. In Protocol 280-10 where the sponsor attempted to determine the pharmacokinetic parameters using the blood concentration values for 0-4 h postdose, total radioactivity exhibited multiexponential kinetics in nine of 10 subjects and monoexponential kinetics in one of 10 subjects. Typical plots of decay-corrected total radioactivity (as %ID versus time) in Figs. 1 and 2 for Protocols 280-10 and 280-11, respectively. Mean plots were not provided. The pharmacokinetic parameters for the studies are presented in Tables 1 and 2, for Protocols 280-10 and 280-11, respectively.

Fig. 1



Gpkplot1 07AUG97 18:51

Figure 2
Plasma Radioactivity Level Over Time
Subject=0004000009



% ID = Percent of injected Tc 99m Dose

0003631

Table 4. Estimates of pharmacokinetic parameters.

Subject Number	$t_{½\alpha}$ (min)	$t_{\beta½}$ (h)	ΔV_C (liters/kg)	ΔV_{DSS} (liters/kg)	Cl_T (ml/min/kg)	Cl_R (ml/min/kg)	Cl_R/Cl_T (%)
Men							
102-4-2	2.7	1.01	0.073	0.150	1.81	1.04	57.1
102-4-4							
102-4-5							
102-4-6							
102-4-7							
102-4-10							
Mean (90% CI)	7 (4 - 48)	1.7 (1.2 - 3.1)	0.090 (0.070 - 0.11)	0.25 (0.11 - 0.39)	1.5 (1.2 - 1.8)	1.2 (1.1 - 1.4)	86 (68 - 105)
Women							
102-4-1							
102-4-3							
102-4-8							
102-4-9							
Mean (90% CI)	8 (3 - ∞)	1.6 (1.1 - 2.6)	0.10 (0.048 - 0.15)	0.26 (0.11 - 0.42)	1.6 (1.3 - 1.9)	1.2 (1.0 - 1.4)	77 (70 - 84)
All Subjects							
Mean (90% CI)	7 (5 - 18)	1.7 (1.3 - 2.2)	0.093 (0.078 - 0.11)	0.25 (0.17 - 0.34)	1.5 (1.4 - 1.7)	1.2 (1.1 - 1.3)	83 (72 - 93)

Values represent individual estimates of pharmacokinetic parameters derived from blood timecourse, along with descriptive statistics by sex and pooled across both sexes. Harmonic means and confidence intervals serve as descriptive statistics for half-lives. The drug conferred only single-compartment pharmacokinetic characteristics in Subject 102-4-1. The upper confidence limit exceeded estimability for alpha half-life for women.

2

Table ~~3.23~~

MEAN AND 90% CI OF PLASMA AND URINE RADIOACTIVITY LEVEL
OF LABELED P280

	T12 (hr)	Kel (/hr)	Vd (ml/kg BW)	Vd_ss (ml/kg BW)	Clearance (ml/min/kg BW)	Cl_ren (ml/min/kg BW)	BOUND (%)
Female							
0002000001							
0002000002							
0002000003							
0004000006							
0004000012							
0004000013							
MEAN	2.0	0.34	389.6	170.2	2.1	0.7	76.3
90% CI		(0.301,0.377)	(267.8,511.4)	(122.2,218.3)	(1.6,2.6)	(-0.3,1.6)	(70.0,82.7)
Male							
0001000001							
0001000002							
0003000001							
0003000002							
0004000001							
0004000002							
0004000003							
0004000004							
0004000005							
0004000007							
0004000008							
0004000009							
0004000010							
0004000011							
MEAN	1.9	0.36	306.1	151.5	1.9	0.7	75.5
90% CI		(0.324,0.405)	(272.1,340.1)	(133.4,169.6)	(1.6,2.1)	(0.3,1.2)	(67.9,83.1)
Total							
MEAN	1.9	0.36	331.1	157.1	1.9	0.7	75.8
90% CI		(0.327,0.387)	(287.2,375.1)	(138.5,175.8)	(1.7,2.2)	(0.3,1.1)	(70.3,81.2)

76.3 ± 8%

75.5 ± 15%

75.8 ± 13%

000332

i. **In normal volunteers**, the overall mean±SD pharmacokinetic parameters were as follows: $t_{1/2}$: 2.53±2.76 h ([n=10], 3.07±3.50 h [n=6] for males and 1.73±0.71 h [n=4] for females); Cl_T: 1.53±0.27 mL/min/kg ([n=10], 1.49±0.32 [n=6] for males and 1.59±0.23 mL/min/kg [n=4] for females); V_c: 0.09±0.03 L/kg ([n=9], 0.09±0.02 L/kg [n=6] for males 0.1±0.03 L/kg [n=3] for females); V_{ss}: 0.25±0.15 L/kg ([n=10], 0.25±0.17 L/kg [n=6] for males and 0.26±0.13 L/kg [n=4] for females; $V_{dß}$: 0.29±0.22 L/kg ([n=10], 0.33±0.29 L/kg [n=6] for males and 0.23±0.07 L/kg [n=4] for females). Based on these SD values, most of the RSD values suggesting that in general, inter individual variability in the kinetics of radioactivity following intravenous doses of Acutect® is low to moderate. However, the RSD values for elimination half-life and V_{ss} and $V_{dß}$ were high due to much higher values of these parameters for Subject 102-4-7 as compared to the other subjects.

ii. **In 18 patients at risk of venous thrombosis and two healthy volunteers** (Protocol 280-11), the overall mean±SD pharmacokinetic parameters were as follows: $t_{1/2}$: 2.0±0.50 h ([n=20], 2.0±.55 h [n=14] for males and 2.1±0.37 h [n=6] for females); Cl_T: 1.9±0.70 mL/min/kg ([n=20], 1.9±0.68 [n=14] for males and 2.1±0.79 mL/min/kg [n=6] for females); V_{ss}: 0.16±0.06 L/kg ([n=20], 0.15±0.04 L/kg [n=14] for males and 0.17±0.13 L/kg [n=6] for females); $V_{dß}$: 0.33±0.12 L/kg ([n=20], 0.31±0.08 L/kg [n=14] for males and 0.39±0.18 L/kg [n=6] for females).

Based on these SD values, the RSD values suggesting that in general, inter individual variability in the kinetics of radioactivity in patients at risk of venous thrombosis receiving intravenous doses of Acutect® is moderate. The findings of these studies (Protocols 280-10 and 280-11) suggest that following intravenous administration od Acutect®, the kinetics of total radioactivity is not affected by gender.

(b) **Urinary Excretion of Radioactivity**: The overall mean±SD amounts of radioactivity ultimately eliminated in urine (cumulative urinary excretion at 22-24 h postdose) was 79.5±5.8%ID ([n-10], 78.5±7.4%ID [n=6] for males and 81.0±2.2%ID [n=4] for females]) for normal volunteers (Protocol 280-10) and 56.7±13.4%ID (n=9 [7 males and 2 females]) for patients at risk of venous thrombosis (Protocol 280-11). The two normal volunteers in Protocol 280-11 were not evaluated for urinary excretion of radioactivity. Complete summaries of the data on the renal excretion profiles of radioactivity in both studies (Protocols 280-10 and 280-11) are presented in Tables 3 and 4.

3

Table ~~5.~~ Cumulative urinary excretion of radioactivity.

Subject Number	Time After Injection (hours)				
	1	2	4	8	22-24
Men					
102-4-2					
102-4-4					
102-4-5					
102-4-6					
102-4-7					
102-4-10					
Mean (90% CI)	34 (28 - 40)	50 (43 - 58)	67 (57 - 77)	75 (68 - 82)	78 (72 - 85)
Women					
102-4-1					
102-4-3					
102-4-8					
102-4-9					
Mean (90% CI)	31 (20 - 43)	49 (41 - 57)	64 (58 -69)	75 (74 - 77)	81 (78 - 84)
All Subjects					
Mean (90% CI)	33 (29 - 38)	50 (45 - 54)	66 (60 - 71)	75 (71 - 79)	79 (76 - 83)

Values are cumulative % ID recovered in urine at the postinjection intervals indicated.

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Table ~~6.24.2~~ 4

**CUMMULATIVE TOTAL URINE EXCRETED Tc 99m OVER TIME
EXPRESSED AS PERCENT OF INJECTED Tc 99m DOSE**

	Hours since Dosing 0-1	0-2	0-4	0-6	0-8	0-12	0-24
Female							
0002000001							
0002000002							
0002000003							
0004000006							
0004000012							
0004000013							
MEAN	3.6	10.7	18.9	29.1	29.2	40.1	40.7
90% CI	(-2.3,9.6)	(5.2,16.2)	(15.7,22.2)	(15.7,42.5)	(15.9,42.4)	(13.4,66.8)	(13.2,68.2)
Male							
0001000001							
0001000002							
0003000001							
0003000002							
0004000001							
0004000002							
0004000003							
0004000004							
0004000005							
0004000007							
0004000008							
0004000009							
0004000010							
0004000011							
MEAN	9.5	23.5	37.0	46.2	52.0	59.3	61.2
90% CI	(5.0,14.0)	(17.8,29.2)	(29.6,44.5)	(39.4,53.0)	(46.7,57.3)	(55.0,63.6)	(57.5,64.9)
Total							
MEAN	8.4	20.9	33.4	42.8	47.4	55.5	56.7
90% CI	(4.5,12.3)	(15.6,26.3)	(26.3,40.5)	(36.0,49.6)	(40.6,54.2)	(48.8,62.2)	(49.3,64.0)

$\bar{X} \pm$ [illegible] 56.6 ± 13.4%   ♀ (n = 2): [illegible] 23.7 [illegible]

♀ (n = 7) range 57 [illegible] 70 [illegible] $\bar{X} \pm$ SD [illegible]   range = 53 [illegible] 65.1

000334

These data suggest (i) that urinary excretion is the major route of Acutect® elimination in healthy individuals and in patients at risk of venous thrombosis and (ii) that in healthy individuals, renal elimination of Acutect® is not affected by gender. Only two female patients were evaluated for urinary excretion of radioactivity; therefore, a gender analysis in this patient population was not feasible. Based on the SD values, the RSD values were 7.3% in normal volunteers (9.4% for males and 2.7% for females) and 13.4% in patients at risk of venous thrombosis. These results suggest low variability in cumulative renal elimination of Acutect® in normal volunteers and in patients at risk of venous thrombosis.

(c) **Biliary excretion of Radioactivity**: In normal volunteers (Protocol 280-10), biliary excretion of radioactivity was estimated as the total amount of radioactivity in the gastrointestinal tract and gallbladder as determined by scintigraphic imaging. The overall mean±SD biliary excretion at 22-24 h postdose was 10.1±2.5%ID ([n=10], 9.6±3.2%ID [n=6] for males and 10.7±2.5%ID [n=4] for females). The SD values represent RSD values ranging from 23% to 33 % suggesting moderate variability of biliary excretion of Acutect® in healthy individuals. The individual subject and mean±SD biliary excretion data are presented in Appendix II (page ///). These results suggest that in healthy individuals, biliary excretion of Acutect® is not affected by gender. In patients at risk of venous thrombosis, the gallbladder was evaluated as an ROI [see page 14, item # d(x)] but the gastrointestinal tract was not. Subsequently, the total amount of radioactivity excreted in the bile could not be determined.

(d) **Radioactivity Contents of Regions of Interest (ROIs)**: For normal volunteers (Protocol 280-10) and in patients at risk of venous thrombosis, (Protocol 280-11), the mean±SD values for the first imaging time (10 min postdose), 4 h post postdose and/or last imaging time (22-24 h) postdose are summarized below. Individual subject data are presented in Appendix II (pages ///-///).

i. **Whole Body**: In normal volunteers, the overall mean±SD was 84.7±5.4%ID ([n=10], 84.9±6.1%ID [n=6] for males and 84.5±5.3%ID [n=4] for females) at 10 min postdose and declined to 23.1±3.9%ID ([n=10], 23.2±4.4%ID [n=6] for males and 23.0±3.8%ID [n=4] for females at 4 h postdose. (Note that these values exclude urinary bladder radioactivity. Upon adding the urinary bladder values for each subject, the whole body radioactivity at 10 min postdoes is 100%ID (since no voiding occurred before this time point).

In patients, the overall mean±SD was 100%ID ([n=20], 100%ID [n=14] for males and 100%ID [n=6] for females) at 10 min postdose and declined to 16.18±4.93%ID ([n=20], 16.2±5.09%ID [n=14] for males and 16.16±5.01%ID [n=6] for females) at 24 h postdose.

ii. **Lung**: In normal volunteers, the overall mean±SD was 4.4±0.6%ID ([n=10], 4.6±0.6%ID [n=6] for males and 4.1±0.7%ID [n=4] for females) at 10 min postdose and declined to 0.8±0.2%ID ([n=10], 0.8±0.2ID% [n=6] for males and 0.7±0.3%ID [n=4] for females) at 4 h postdose. Radioactivity was not detected at 22-24 h postdose. In patients, the overall mean±SD was 8.42±1.68%ID ([n=20], 8.86±1.63%ID [n=14] for males and 7.41±1.42%ID [n=6] for females) at 10 min postdose and declined to 0.67±0.30%ID ([n=20],

0.77±0.29%ID [n=14] for males and 0.42±0.10%ID for females) at 24 h postdose.

iii. **Heart**: In normal volunteers, the overall mean±SD was 3.5±0.8%ID ([n=10], 3.3±0.6%ID [n=6] for males and 3.8±0.9%ID [n=4] for females) at 10 min postdose and declined to 0.5±0.1%ID ([n=10], 0.6±0.1%ID [n=6] for males and 0.5±0.2%ID [n=4] for females) at 4 h postdose. Radioactivity was not detected at 22-24 h postdose. In patients, the overall mean±SD was 2.76±0.60%ID ([n=20], 2.82±1.83%ID [n=14] for males and 2.62±0.34%ID [n=6] for females) at 10 min postdose and declined to 0.20±0.08%ID ([n=20], 0.22±0.08%ID [n=14] for males and 0.6±0.05%ID [n=6] for females) at 24 h postdose.

iv. **Spleen**: In normal volunteers, the overall mean±SD was 1.5±0.5%ID ([n=10], 1.6±0.4%ID [n=6] for males and 1.5±0.7%ID [n=4] for females) at 10 min postdose and declined to 0.4±0.2%ID ([n=20], 0.4±0.2% [n=14] for males and 0.5±0.2%ID [n=6] for females) at 4 h postdose. Radioactivity (0.1%ID) was detected only in one male, normal volunteer at 22-24 h postdose. In patients, the overall mean±SD was 1.02±0.35%ID ([n=20], 0.98±0.36%ID [n=14] for males and 1.13±0.36%ID [n=6] for females) at 10 min postdose and declined to 0.48±0.49%ID ([n=20], 0.39±0.38%ID [n=14] for males and 0.68±0.69%ID [n=6] for females) at 24 h postdose.

v. **Breast (Normal Female Volunteers only)**: The mean±SD was 4.4±1.2%ID (n=4) at 10 min postdose and declined to 1.0±0.8%ID (n=4) at 4 h postdose. Radioactivity was not detected at 22-24 h postdose.

vi. **Liver**: In normal volunteers, the overall mean±SD was 10.1±1.2%ID ([n=10], 9.8±1.0%ID [n=6] for males and 10.6±1.4%ID [n=4] for females) at 10 min postdose and declined to 1.8±0.5%ID ([n=10], 1.8±0.3%ID [n=6] for males and 2.0±0.7%ID [n=4] for females) at 22-24 h postdose. In patients, the overall mean±SD was 6.56±1.61%ID ([n=20], 6.11±1.17%ID [n=14] for males and 7.63±2.09%ID [n=6] for females) at 10 min postdose and declined to 1.17±0.54%ID ([n=20], 1.07±0.51%ID for males [n=14] and 1.39±0.59%ID [n=6] for females) at 24 h postdose.

vii. **Kidneys**: In normal volunteers, the overall mean±SD was 7.3±1.8%ID ([n=10], 6.2±0.9%ID [n=6] for males and 8.9±1.6%ID [n=4] for females) at 10 min postdose and declined to 1.9±0.5%ID ([n=10], 1.8±0.2%ID [n=6] for males and 2.1±0.8%ID [n=4] for females) at 4 h postdose. Radioactivity (1.6%ID) was detected only in one healthy, male volunteer at 22-24 h postdose. In patients, the overall mean±SD was 5.95±2.06%ID ([n=20], 5.60±1.46%ID [n=14] for males and 6.75±3.09%ID [n=6] for females) at 10 min postdose and declined to 2.19±1.30%ID ([n=20], 1.86±1.10%ID [n=14] for males and 2.97±1.49%ID [n=6] for females) at 24 h postdose.

viii. **Urinary Bladder**: In normal volunteers, the overall mean±SD was 15.3±5.4%ID ([n=10], 15.60±6.0%ID [n=6] for males and 15.5±5.3%ID [n=4] for females) at *10 min* postdose. The urinary bladder was not evaluated at any other time postdose in these subjects. In patients, the overall mean±SD was 11.63±4.25%ID ([n=20], 10.97±4.00%ID [n=14] for

males and 13.18±4.82%ID [n=6] for females) at 10 min postdose and declined to 0.52±0.60%ID ([n=20], 0.57±0.70%ID [n=14] for males and 0.41±0.27%ID [n=4] for females) at 24 h postdose.

ix. **Brain**: In patients, the overall mean±SD was 1.17±0.27%ID ([n=19], 1.21±0.29%ID [n=13] for males and 1.08±0.20%ID [n=6] for females) at 10 min postdose and declined to 0.13±0.05%ID ([n=20], 0.14±0.05%ID for males [n=14] and 0.09±0.03%ID [n=6] for females) at 24 h postdose. The brain was not evaluated in normal volunteers.

x. **Gallbladder**: In patients, the overall mean±SD was 0.55±0.52%ID ([n=20], 0.46±0.37%ID [n=14] for males and 0.44±0.77%ID [n=6] for females) at 10 min postdose and declined to 0.19±0.26%ID ([n=20], 0.16±0.18%ID [n=14] for males and 0.25±0.41%ID [n=6] for females) at 24 h postdose. In normal volunteers, the gallbladder was evaluated along with the gastrointestinal tract (see item #1(c) [Biliary Excretion of radioactivity above]).

xi. **Abdomen**: In patients, the overall mean±SD was 15.38±3.39%ID ([n=20], 15.67±3.67%ID [n=14] for males and 14.71±8.82%ID [n=6] for females) at 10 min postdose and declined to 5.85±2.72%ID ([n=20], 5.74±2.82%ID [n=14] for males and 6.11±2.70%ID [n=6] for females) at 24 h postdose. In normal volunteers, the abdomen was not evaluated as a single region of interest.

For normal volunteers, most of the SDs for the ROIs represent RSD values , suggesting that in general, following intravenous doses of Acutect®, inter individual variability in amounts of radioactivity in the ROIs is low to moderate. In patients, RSD values in most cases also suggesting low to moderate variability in the related amounts of radioactivity. However, higher variability was observed in some cases (RSD was at 24 h postdose for abdomen, kidneys and liver, at 24 h postdose for the spleen, at 10 min postdose and at 24 h postdose for the gall bladder). The high inter individual variability in the amounts of radioactivity in the gallbladder of these patients suggests high individual inter individual variability of biliary excretion of radioactivity.

In general, the ROI data suggest that following intravenous administration of Acutect® to normal volunteers or patients, (i) only a small fraction of total radioactivity is present in any internal organ at any given time (≤24.2%ID in the kidneys [the excretory organ] at 10 min postdose and ≤12.0%ID in any other organ at any time postdose in healthy volunteers or patients), (ii) the amounts of radioactivity that enter the body organs disappear rapidly from most internal organs, and (iii) that in healthy individuals or patients, within 24 hours of intravenous Acutect® administration, there appears to be no effect of gender in the amounts of radioactivity present in the body organs covered under item #d (pages 12-14) above.

2. PHARMACOKINETICS OF UNLABELLED PEPTIDE: An evaluation of the unlabelled P280 peptide was attempted in Protocol 280-11 using the method. This method measured mainly P1007. In the NDA, it is stated that the method was used to determine that this peptide (P1007) constituted 65% of the administered peptide dose (see page 2 of this review).

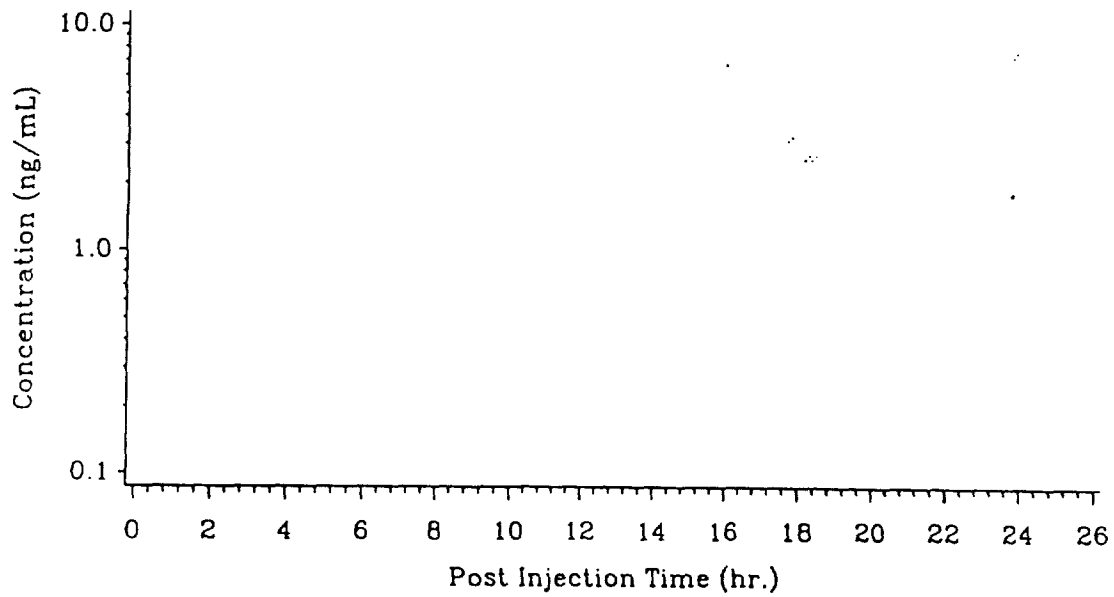
P1007 was not detectable in at least 50% of the subjects after 6 h postdose or in any subject after 12 h postdose (see Appendix II [page ///]). A typical plasma concentration versus time curve is presented in Figures 3. Due to the erratic nature of the curves, a pharmacokinetic evaluation of the peptide was not performed. The erratic nature of the curve suggests enterohepatic cycling of the peptide. Urinary excretion of P1007 was evaluated in **17 of 20 subjects and of the total peptide dose for a 24 h period** (see Appendix II [page ///]). A mean value and standard deviation would be misleading due to some missing data for some of the subjects.

Technetium Tc 99m P280 (Diatide Inc.)
Protocol P280-11
Clinical/Statistical Report

Gpkplot2 07AUG97 18:51

Figure 3

Plasma Concentration of P280 Over Time
Subject=0001000002



Concentration expressed as ng P1007 equivalents/mL
Concentration less than lowest detectable limit is excluded

200002

3. METABOLISM OF RADIOACTIVE PEPTIDE: The presence of radioactive metabolites in the blood or urine of subjects receiving Acutect® was assessed by a reverse phase HPLC method with fraction collection (Protocol 280-11). Two unidentified, radioactive metabolites, both more polar than the parent drug were observed in urine (see Appendix II [page ///]). The more polar of the two metabolites was estimated at ≤10% of total radioactivity while the other metabolite was estimated at ≤30% of total radioactivity. The more polar metabolite was also detected in plasma. Literature information indicates that protein drugs with MW ≤30,000 daltons tend to be filtered in the in the glomeruli of the kidneys, taken up by the cells of the proximal tubules of the kidney and metabolized and that very little amounts of such drugs are eliminated unchanged in the urine. This suggests (i) that the kidney may be the major site of metabolism of ^{99m}Tc technetium apcitide as well as the site of its eventual elimination from the body and (ii) that the radioactivity detected in the urine following Acutect administration may represent predominantly ^{99m}Tc technetium apcitide metabolites. The in vitro study of the metabolism of ^{3}H-labelled apcitide, P1007 and P1008 in rat rabbit and human slices did not yield any further insight into the metabolism of these peptides, subsequently, a comprehensive review of this study was not necessary.

4. PLASMA PROTEIN BINDING: In vivo plasma protein binding of total radioactivity in patients was determined by the centrifuge-assisted ultrafiltration method using the 30 min plasma sample (Protocol 280-11). The mean±SD plasma protein binding was 75.8±13.4% ([n=16], 75.5±15.4% [n=11] for males and 76.3±8.7% [n=5] for females). Individual subject plasma protein data are provided on page 8. These results suggest that in patients receiving single intravenous doses of Acutect®, plasma protein binding of radioactivity is not affected by gender.

5. FOOD EFFECT: No studies were conducted to evaluate the effect of food on the disposition of Acutect®. Such studies are not necessary since the drug is indicated for intravenous administration.

6. GENDER DIFFERENCES: As covered under items 1-6 above, the information provided in the NDA suggests that gender has no significant effect in the disposition of Acutect®.

7. SPECIAL POPULATIONS:

(a) **Patients with Impaired Renal Function**: No studies were conducted to evaluate the disposition of Acutect® in patients with impaired function. In Protocol 280-11, the serum creatinine of one patient (Patient 0004000007) was , (normal range for the study: <1.5 mg/dL). The percentage of the injected radioactivity eliminated in urine in 24 hours by this patient (59.9%) was within the range eliminated in the same time interval by patients with serum creatinine less than 15 mg/dL . **In the proposed package insert, under Dosage and Administration, it is stated that dosage adjustment has not been established in patients with renal insufficiency.** Literature information indicates that protein drugs of the molecular size of apcitide are significantly metabolized in the kidney. Therefore, it appears that for ^{99m}Tc apcitide, the kidney could be a major organ of metabolism as well as the organ of eventual elimination®. Due to the paramount role that the kidneys might play in the elimination

of this drug, a study in renally impaired subjects has been suggested as covered under General Comment 1.

(b) **Geriatric Patients**: Six of the nine patients (five males and one female) in whom 24 h cumulative urinary excretion of radioactivity was evaluated (Protocol 280-11) were in the age For these geriatric patients, the mean±SD cumulative urinary radioactivity elimination was 58.8±4.5% of the administered radioactivity dose (range=53.7-65.1%) versus 56.6±13.4% for all evaluated patients. The 24 h cumulative urinary excretion of radioactivity for the only female geriatric patient (57.4%) was within the range for the male geriatric patients). For the three patients under 65 years old, the 24 h cumulative %ID eliminated in urine were 23.9%, 59.9% and 70%). For the geriatric patients (n=9) evaluated for pharmacokinetic parameters and plasma protein binding in this study, the pharmacokinetic parameters and plasma protein binding were similar to those of the patients under 65 years of age (see Table 2 [page 8]). Thus in this study, the six geriatric patients evaluated were similar to the patients under 65 years of age in urinary excretion, plasma protein binding and pharmacokinetic parameters of total radioactivity following intravenous injection of Acutect®. **In the proposed package insert, under Dosage and Administration, the sponsor states that dosage adjustment has not been established in geriatric patients.**

(c) **Pediatric Patients**: Studies have not been conducted to assess the disposition of Acutect® in pediatric patients. **In the proposed package insert, (i) under Pediatric Use, it is stated that "safety and effectiveness [of Acutect®] in pediatric patients have not been established" and (ii) under Dosage and Administration, it is stated that dosage adjustment has not been established in pediatric patients.**

8. DRUG-DRUG INTERACTIONS: No pharmacokinetic studies were conducted to assess possible interactions of Acutect® with any concomitantly administered drug. In the proposed package insert, under **Drug Interactions**, it is stated that "**drug interactions were not noted in clinical studies in which technetium Tc 99m apcitide was administered to patients receiving concomitant medications**". In the NDA, it is stated that the "**concomitant medications**" included the antithrombotic agents, warfarin (99% plasma protein bound), heparin (extensively plasma protein bound), acetylsalicylic acid and enoxaparin (Protocol 280-11). No quantitative data from the "**clinical studies**" were provided to support this statement.

9. PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) RELATIONS:
In the proposed package insert, it is recommended that "**imaging be performed 10 to 60 minutes following administration of the agent**" suggesting that optimal image quality is obtained within the specified time interval. In patients (Protocol 280-11), this time interval corresponds to ≥62.5±15.3%ID (n=14) in plasma at imaging time. In the **Adverse Events** section of the proposed package insert, it is stated that in clinical studies evaluating 684 adults (53% men and 47% women, receiving a mean dose of 20 mCi of ^{99m}Tc technetium and 76.3 μg of bibapcitide, adverse events were observed in less than 6%. The adverse events were specified as follows: pain (1%), headache, asthenia, back pain, chest pain, hypotension, nausea, and hypertension. The sponsor also states that two of 161

subjects (1.2%) evaluated for clinical laboratory parameters experienced **clinically significant increases** in GGT. It is further stated that **clinically significant abnormalities** were noted in the following hematological/serum chemistry parameters in less than 1% of the 161 subjects evaluated: WBC, total iron, ALT, AST and phosphatase. The time of observation relative to Acutect® administration or duration of occurrence was not stated for any of the adverse events, abnormal clinical laboratory parameters or abnormal hematological parameters. The amounts or concentrations of Acutect® in the blood or plasma at the time of these events were also not provided. Therefore, a relationship could not be established between the amount/concentration of the drug in the blood or tissues and the adverse events or abnormal values of clinical laboratory/hematological parameters observed in the clinical studies.

10. DOSIMETRY: RADIATION ABSORBED DOSE: In the proposed package insert, under **Radiation Dosimetry**, the sponsor provides a table of mean **estimated absorbed radiation dose for specific organs of to an average (70 kg) adult from an intravenous injection of Acutect®**. The values were based on urinary bladder emptying at 4.8 h postdose. The limits of organ absorbed radiation from administered radionuclide doses **"for certain research uses" are specified as follows: for "whole body, active blood-forming organs lens of the eye and gonads": ≤3 rems from a "single dose" and 5 rem for "annual and total dose commitment"; for other organs": ≤ 5 rem from a "single dose" and 15 rem for "annual and total dose commitment"** (21 CFR 361.1)(b)(3). The absorbed radiation dose stated for each organ in the proposed package insert is within the limits specified in the CFR for a single radionuclide dose administration. The dosimetry data provided by the sponsor is presented in Appendix II (page ///).

11. SAMPLE ANALYSIS: See Appendix I (pages 23 and 26).

12. PHARMACOKINETIC ANALYSIS: See Appendix I (pages 23 and 27).

13. FORMULATION: The compositions of Acutect® is presented in Appendix II (page ///).

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ON ORIGINAL

III LABELING COMMENTS

1. The following comments are related to the **pharmacokinetics** component of the **proposed package insert**:

(a) The pharmacokinetic parameters of Acutect® in patients at risk of venous thrombosis (the target population), that were obtained based on data covering more than three half-lives of the drug, are considered even more pertinent than those obtained in normal volunteers. Therefore, they need to be included in the package insert. The pharmacokinetc parameters in normal volunteers may also be included with the statement that they were based on blood data for the time interval of 0-4 h postdose". The apparent volumes of distribution should be stated in volume units. The values relative to body weight may then be provided as additional information.

(b) It is stated that in patients with **"limited renal function impairment (serum creatinine of 1.5 to 1.7 mg%) the "total clearance of this tracer"** was not affected. This statement relates to Protocol 280-11. The cohort of patients referred to consisted of only two patients (Patient 0002000001 and 0007000007 with serum creatinine values of , respectively, [NDA Volume 1.21 {pages 247-248}]). Renal elimination of radioactivity was determined only for Patient 0004000007 and the cumulative value at 24 h postdose was 59.9%ID. In this study, the range of radioactivity eliminated in urine was). Therefore, the above statement should be modified to indicate that **in a study of renal excretion of total radioactivity in nine patients receiving the package insert dose of Acutect®, the amount of radioactivity eliminated in the only evaluated patient with limited impairment of renal function (serum creatinine=1.7 mg/dL) was 59.9%ID, which was within the range of values for the eight evaluated patients with normal renal function** .

2. In the package insert, under the sub-section of **metabolism**, the number of patients (n=18) and normal volunteers (n=2) referred to in the opening statement should be stated.

IV. GENERAL COMMENT

1. Literature information indicates that protein drugs with molecular weights of 30,000 daltons or less tend to be filtered in the glomeruli of the kidneys, taken up by the cells of the proximal tubules of the kidney and metabolized and that very little amounts of such drugs are eliminated unchanged in the urine. Based on this information, the kidney may be the major site of metabolism of ^{99m}Tc technetium apcitide as well as the site of its eventual elimination from the body. The unlabeled peptide is also eliminated in urine. In the pharmacokinetic studies, no information was provided on the disposition of Acutect® in renally impaired subjects. Such information would be the basis for developing appropriate statements of precaution, warning or contraindication related to this patient population in the package insert. Accordingly, it is recommended that pharmacokinetic data be obtained in this patient population. However, if renally impaired patients were included in the well controlled clinical studies and the safety profile in this population was comparable to that of renally normal patients, HFD-160 may use its discretion and decide whether or not the requested study is necessary.

2. The optimal imaging time stated in the package insert is 10-60 min following Acutect® administration. In patients (Protocol 280-11), this time interval corresponds to $\geq 62.5 \pm 15.3$%ID (n=14) in plasma at imaging time. Thus, it appears that for a dose lower than the package insert recommended dose (e.g., 70% of the package insert dose) images of good quality could still be obtained in the early part of the imaging time interval (e.g., 10-25 min postdose). This principle could be used for lowering the dose for patients with certain degrees of renal impairment. This could be discussed with the sponsor if it is deemed appropriate.

3. Based on the plots of %ID in blood versus time provided in the NDA, it appears that for normal volunteers (Protocol 280-10) the pharmacokinetic parameters were derived from data obtained for the sample collection interval of 0-4 h postdose which is less than three half-lives of decay corrected total radioactivity. Ideally, the samples should be collected for at least three half lives of the drug for the pharmacokinetic parameters to be considered valid. However, since (i) pharmacokinetic parameters were satisfactorily determined in patients (Protocol 280-11) and (ii) the pharmacokinetic parameters in normal volunteers appear to be similar to those obtained in patients, it is considered reasonable to refrain recommending that another pharmacokinetic study be conducted in normal volunteers. The use of the pharmacokinetic parameters obtained in this study has already been covered in Labeling Comment 1(a).

4. AUC values were not provided in any of the pharmacokinetic studies (Protocol 280-10 or 280-11). Since Acutect® is administered intravenously, the extent of systemic availability is not in question. Since its elimination can be satisfactorily characterized using its elimination half-life and clearance, it is considered reasonable to refrain from asking the sponsor to provide the AUC values or for this reviewer to compute it as a part of the review process.

5. For the . analysis of unlabelled peptide, the precision and accuracy of the assay method were not provided. Since pharmacokinetic parameters were not derived from the . data, it is considered reasonable to refrain from asking the sponsor to submit the precision and accuracy data for the assay method.

6. Information that would allow for an evaluation of the individual radioactive moieties (i.e., parent drug and metabolites) beyond 6 h postdose in plasma and 4 h postdose in urine was not provided in the NDA.

V. RECOMMENDATION

NDA 20-887, for ^{99m}Tc technetium apcitide (Acutect®) submitted by the sponsor on August 20, 1997, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. From a clinical pharmacokinetic perspective, the NDA is considered approvable. However, the issues raised in Labeling Comments 1 and 2 (page 19) need to be satisfactorily addressed by the sponsor.

Please convey this Recommendation and Labeling Comments 1 and 2 (page 19), as appropriate, to the sponsor. General Comments 1 and 2 (page 20) should be brought to attention of the reviewing medical officer for consideration regarding possible further contacts with the sponsor.

Appendices I and II are retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

APPEARS THIS WAY
ON ORIGINAL

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee, Ph.D. _____

FT Initialed by David Lee, Ph.D. _____

Clinpharm/Biopharm Briefing: /////// at ////// in PKLN Room (Attendees: ////////////////////////)

cc: NDA 20-887, HFD-160, HFD-160 (Ferre-Hockensmith), HFD-850 (Huang), HFD-870 (M. Chen, Hunt, Lee and Udo), CDR (Attn: Barbara Murphy).

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ON ORIGINAL

Table 7. Scintigraphic estimates of % ID in body, gastrointestinal tract (including gall bladder) and urinary bladder.

Subject	Body				Gastrointestinal Tract				Bladder
Number	10 min	1 h	2 h	4 h	1 h	2 h	4 h	22-24 h	10 min
Men									
102-4-2									
102-4-4									
102-4-5									
102-4-6									
102-4-7									
102-4-10									
Mean (90% CI)	85 (80 - 90)	58 (55 - 61)	41 (40 -43)	23 (20 - 27)	3.0 (1.9 - 4.2)	4.8 (2.2 - 7.4)	7.8 (5.8 - 9.8)	9.6 (7.0 - 12.2)	15.2 (10.2 - 20.1)
	80.9 ± 6.1			23.2	± 1.4			± 3.2 (33 %)	15.2 ± 6.0
Women	7.7 %) (			± 4.5 %)	46.7 %				(39.5 %)
102-4-1									
102-4-3									
102-4-8									
102-4-9									
Mean (90% CI)	85 (78 - 91)	57 (52 - 63)	38 (32 - 44)	23 (19 - 28)	3.8 (1.7 - 6.0)	5.0 (0.0 - 10.3)	8.8 (6.0 - 11.6)	10.7 (7.8 - 13.6)	15.5 (9.2 - 21.7)
	80.5 ± 5.3			23.0 ± 3.8				± 2.5 (23 %)	± 5.3
All Subjects	6.3 %			(16.5 %)					34.2 %)
Mean (90% CI)	85 (82 - 88)	58 (56 - 60)	40 (38 - 42)	23 (21 - 25)	3.4 (2.5 - 4.3)	4.9 (2.9 - 6.9)	8.2 (6.8 - 9.5)	10.1 (8.4 - 11.7)	15.3 (12.1 - 18.4)
	84.7 ± 5.4 (6.4 %)			23.1 ± 3.9 (16.9 %)				± 2.8 %	± 5.4 (35.3 %)

Values represent % ID at the nominal times after injection indicated in the whole-body ROI (deducting that in the urinary bladder and gastrointestinal tract & gall bladder), gastrointestinal tract and gall bladder combined, and in urinary bladder. Scintigraphy could not visualize whole-body at the 22- to 24-hour interval, and did not visualize gall bladder and gastrointestinal tract activity at 10 minutes. After 10 minutes, subjects urinated; thus, % ID in bladder did not reflect urinary excretion quantitatively thereafter.

Table 8a. Scintigraphic estimation of % ID in visualized organs—Lung.

Subject Number	Nominal Time After Injection				
	10 min	1 h	2 h	4 h	22 - 24 h
Men					
102-4-2					Not Visualized
102-4-4					Not Visualized
102-4-5					Not Visualized
102-4-6					Not Visualized
102-4-7					Not Visualized
102-4-10					Not Visualized
Mean (90% CI)	4.5 (4.0 - 5.0)	3.0 (2.7 - 3.3)	1.8 (1.6 - 2.0)	0.8 (0.7 - 0.9)	
	4.6 ± 0.6 (13.0%)			0.2 (25%)	
Women					
102-4-1					Not Visualized
102-4-3					Not Visualized
102-4-8					Not Visualized
102-4-9					Not Visualized
Mean (90% CI)	4.1 (3.3 - 4.9)	2.2 (1.8 - 2.6)	1.4 (1.1 - 1.7)	0.7 (0.4 - 1.0)	
	±0.7 (17.1%)			±0.3 (42.9%)	
All Subjects					
Mean (90% CI)	4.4 (4.0 - 4.7)	2.7 (2.4 - 3.0)	1.6 (1.4 - 1.8)	0.8 (0.6 - 0.9)	
	±0.6 (13.6%)			0.2 (25%)	

Values represent % ID in the ROI at the specified nominal times after injection.

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Table 8b. Scintigraphic estimation of % ID in visualized organs—Heart.

Subject Number	Nominal Time After Injection				
	10 min	1 h	2 h	4 h	22 - 24 h
Men					
102-4-2					Not Visualized
102-4-4					Not Visualized
102-4-5					Not Visualized
102-4-6					Not Visualized
102-4-7					Not Visualized
102-4-10					Not Visualized
Mean (90% CI)	3.3 (2.8 - 3.8) ±0.6 (18.1)	1.9 (1.6 - 2.1) ±0.3 (15.8 %)	1.2 (1.0 - 1.3)	0.6 (0.5 - 0.7) ±0.1 (16.7 %)	
Women					
102-4-1					Not Visualized
102-4-3					Not Visualized
102-4-8					Not Visualized
102-4-9					Not Visualized
Mean (90% CI)	3.8 (2.7 - 4.9) ±0.9 (23.7 %)	1.9 (1.3 - 2.6)	1.0 (0.6 - 1.5)	0.5 (0.3 - 0.7) ±0.2 (40 %)	
All Subjects					
Mean (90% CI)	3.5 (3.1 - 3.9) ±0.8 (22.9 %)	1.9 (1.7 - 2.1)	1.1 (1.0 - 1.2)	0.5 (0.5 - 0.6) ±0.1 (20 %)	

Values represent % ID in the ROI at the specified nominal times after injection.

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Table 8c. Scintigraphic estimation of % ID in visualized organs—Spleen.

Subject Number	Nominal Time After Injection				
	10 min	1 h	2 h	4 h	22 - 24 h
Men					
102-4-2					Not Visualized
102-4-4					Not Visualized
102-4-5					Not Visualized
102-4-6					Not Visualized
102-4-7					Not Visualized
102-4-10					0.1
Mean (90% CI)	1.6 (1.3 - 1.9) ±0.4 (25%)	0.9 (0.7 - 1.2)	0.6 (0.5 - 0.8)	0.4 (0.2 - 0.6) ±0.2 (50%)	
Women					
102-4-1					Not Visualized
102-4-3					Not Visualized
102-4-8					Not Visualized
102-4-9					Not Visualized
Mean (90% CI)	1.5 (0.6 - 2.3) ±0.7 (46.7%)	1.1 (0.7 - 1.6)	0.6 (0.6 - 0.6)	0.4 (0.3 - 0.4) ±0.1 (25%)	
All Subjects					
Mean (90% CI)	1.5 (1.2 - 1.8) ±0.5 (33.3%)	1.0 (0.8 - 1.2)	0.6 (0.5 - 0.7)	0.4 (0.3 - 0.5) ±0.2 (50%)	

Values represent % ID in the ROI at the specified nominal times after injection.

Table 8d. Scintigraphic estimation of % ID in visualized organs—Breasts.

Subject Number	Nominal Time After Injection				
	10 min	1 h	2 h	4 h	22 - 24 h
Women					
102-4-1					Not Visualized
102-4-3					Not Visualized
102-4-8					Not Visualized
102-4-9	Not Visualized				Not Visualized
Mean (90% CI)	4.3 (2.4 - 6.3)	2.5 (1.1 - 3.8)	1.9 (0.7 - 3.1)	1.0 (0.1 - 1.9)	
	4.4 ± 1.2 (27.3%)			±0.8 (80%)	

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Values represent % ID in the ROI at the specified nominal times after injection. Scintigraphy did not visualize any radioactivity in breasts in men.

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Table 8e. Scintigraphic estimation of % ID in visualized organs—Liver.

Subject Number	Nominal Time After Injection				
	10 min	1 h	2 h	4 h	22 - 24 h
Men					
102-4-2					
102-4-4					
102-4-5					
102-4-6					
102-4-7					
102-4-10					
Mean (90% CI)	9.8 (9.0 - 10.7) ±1.0 (10.2%)	6.6 (5.8 - 7.5)	4.7 (4.2 - 5.2)	2.4 (2.0 - 2.9)	1.8 (1.5 - 2.0) ±0.3 (16.7%)
Women					
102-4-1					
102-4-3					
102-4-8					
102-4-9					
Mean (90% CI)	10.6 (9.0 - 12.2) ±1.4 (13.2%)	8.3 (6.7 - 9.9)	5.6 (4.5 - 6.7)	3.0 (1.8 - 4.3)	2.0 (1.1 - 2.8) ±0.7 (35.0%)
All Subjects					
Mean (90% CI)	10.1 (9.4 - 10.8) ±1.2	7.3 (6.5 - 8.1)	5.1 (54.6 - 5.5)	2.7 (2.2 - 3.1)	1.8 (1.6 - 2.1) ±0.5 (27.8%)

Values represent % ID in the ROI at the specified nominal times after injection.

Table 8f. Scintigraphic estimation of % ID in visualized organs—Kidney.

Subject Number	Nominal Time After Injection				
	10 min	1 h	2 h	4 h	22 - 24 h
Men					
102-4-2					Not Visualized
102-4-4					Not Visualized
102-4-5					Not Visualized
102-4-6					Not Visualized
102-4-7					Not Visualized
102-4-10					1.6
Mean (90% CI)	6.2 (5.5 - 6.9) ±0.9 (14.5%)	4.2 (3.8 - 4.6)	3.1 (2.5 - 3.7)	1.8 (1.6 - 1.9) ±0.2 (11.1%)	
Women					
102-4-1					Not Visualized
102-4-3					Not Visualized
102-4-8					Not Visualized
102-4-9					Not Visualized
Mean (90% CI)	8.9 (7.1 - 10.8) ±1.6 (18.0%)	5.9 (4.9 - 7.0)	3.7 (2.6 - 4.8)	2.1 (1.1 - 3.1) ±0.8 (38.1%)	
All Subjects					
Mean (90% CI)	7.3 (6.3 - 8.3) ±1.8 (24.7%)	4.9 (4.2 - 5.5)	3.3 (2.9 - 3.8)	1.9 (1.6 - 2.2) ±0.5 (26.3%)	

Values represent % ID in the ROI at the specified nominal times after injection for both kidneys, estimated by taking the activity in left kidney's ROI (right kidney's ROI often contains interference from liver) and multiplying by 2.

Table S.28.1

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=ABDOMEN

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN±SD	14.71 ±2.82 (19 %)	12.28	10.84	9.55	6.11 ±2.70 (44 %)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003					
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	15.67 ±3.67 (23 %)	12.33	10.73	9.33	5.74 ±2.82 (49 %)
Total					
MEAN	15.38 ±3.39 (22 %)	12.31	10.76	9.40	5.85 ±2.72 (46 %)

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Table S.28.2

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=BLADDER

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN	13.18 ± 4.82 (37%)	24.14	20.71	8.69	0.41 ± 0.27 (66%)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003					
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	10.97 ± 4.00 (36%)	10.52	6.41	5.51	0.57 ± 0.70 (123%)
Total					
MEAN	11.63 ± 4.25 (37%)	14.60	10.17	6.46	0.52 ± 0.60 (115%)

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Table S.28.3

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=BRAIN

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN	1.08 ± 0.20 (19%)	0.67	0.44	0.22	0.09 ± 0.03 (38%)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003	??				
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	1.12 1.21±0.29 (24%)	0.78	0.54	0.29	0.14 ± 0.05 (36%)
Total					
MEAN	1.11 1.17±0.27 (23%)	0.75	0.51	0.27	0.13 ± 0.05 (38%)

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Table S.28.4

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=GALLBLADDER

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN	0.78 ± 0.77 (99%)	0.89	0.90	0.62	0.25 ± 0.41 (164%)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003					
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	0.46 ± 0.37 (80%)	0.61	0.67	0.48	0.16 ± 0.18 (113%)
Total					
MEAN	0.55 ± 0.52 (95%)	0.70	0.73	0.52	0.19 ± 0.26 (137%)

Table S.28.5

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=HEART

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN	2.61 ± 0.34 (13%)	1.72	1.17	0.49	0.16 ± 0.05 (31%)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003					
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	2.82 ± 0.68 (24%)	1.78	1.25	0.75	0.22 ± 0.08 (36%)
Total					
MEAN	2.76 ± 0.60 (22%)	1.76	1.23	0.67	0.20 ± 0.08 (40%)

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Table S.28.6

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=KIDNEYS

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN	6.75 ± 3.09 (46%)	5.17	4.21	2.97	2.97 ± 1.49 (50%)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003					
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	5.60 ± 1.46 (26%)	4.35	3.43	2.72	1.86 ± 1.10 (59%)
Total					
MEAN	5.95 ± 2.06 (35%)	4.60	3.63	2.80	2.19 ± 1.30 (59%)

Table S.28.7

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=LIVER

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN	7.63 ± 2.09 (27%)	6.09	4.63	2.81	1.34 ± 0.59 (42%)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003					
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	6.11 ± 1.17 (19%)	4.72	3.74	2.34	1.07 ±0.51 (48%)
Total					
MEAN	6.56 ± 1.61 (25%)	5.13	3.98	2.48	1.17 ± 0.54 (46%)

Table S.28.8

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=LUNGS

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN	7.41 ± 1.42 (19%)	4.94	3.37	1.74	0.42 ± 0.10 (24%)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003					
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	8.86 ± 1.63 (18%)	5.91	4.27	2.50	0.77 ± 0.29 (38%)
Total					
MEAN	8.42 ± 1.68 (20%)	5.62	4.03	2.27	0.67 ± 0.30 (45%)

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Table S.28.9

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=SPLEEN

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN	1.13 ± 0.36 (32%)	0.79	0.55	0.33	0.68 ± 0.69 (101%)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003					
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	0.98 ± 0.36 (37%)	0.68	0.50	0.34	0.39 ± 0.38 (97%)
Total					
MEAN	1.02 ± 0.35 (34%)	0.71	0.52	0.34	0.48 ± 0.49 (102%)

Table S.28.10

SUMMARY OF RADIOACTIVITY OF TECHNETIUM Tc 99m P280 FOR AREA OF INTEREST
AREA=WHOLEBODY

	10 Minutes	1 Hour	2 Hours	4 Hours	24 Hours
Female					
0002000001					
0002000002					
0002000003					
0004000006					
0004000012					
0004000013					
MEAN	100.00	93.00	76.14	43.87	16.13 ±5.01 (31%)
Male					
0001000001					
0001000002					
0003000001					
0003000002					
0004000001					
0004000002					
0004000003					
0004000004					
0004000005					
0004000007					
0004000008					
0004000009					
0004000010					
0004000011					
MEAN	100.00	80.82	62.18	44.16	16.20 ±5.09 (31%)
Total					
MEAN	100.00	84.47	65.85	44.07	16.18 ±4.93 (30%)

Table 4. Estimated absorbed radiation dose

Target Organ	rad/mCi	mGy/MBq
Urinary Bladder Wall	0.22	0.060
Kidneys	0.050	0.014
Uterus	0.034	0.0093
Lower Large Intestine Wall	0.037	0.010
Upper Large Intestine Wall	0.039	0.010
Breasts	0.0050	0.0013
Testes/Ovaries	0.020/0.023	0.0053/0.0063
Lungs	0.016	0.0043
Red Marrow	0.0091	0.0025
Thyroid Gland	0.022	0.0060

Dose calculations were performed using the standard MIRD method (MIRD Pamphlet No. 1 rev., Soc. Nucl. Med., 1976). Effective dose equivalent was calculated in accordance with ICRP 53 (Ann. ICRP 18, 14, 1988) and gave a value of 0.010 mSv/MBq (0.037 rem/mCi).

Instructions for the preparation of technetium Tc 99m apcitide

Use aseptic technique throughout. The user should wear waterproof gloves and use shielding at all times when handling the reconstituted vial or syringes containing the radioactive agent.

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The patient doses should be measured using a suitably calibrated radioactivity dose meter immediately prior to administration to the patient.

1. Prepare a rolling-boil water bath containing a lead vial shield standing in and equilibrated with the boiling

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2.D.3. Drug Product

Kit for the Preparation to Technetium Tc 99m Apcitide is a single-dose, lyophilized product in a 10 mL USP Type I glass tubing vial with a 20 mm gray butyl rubber lyophilization stopper sealed with an aluminum crimp cap. Prior to use, the drug product is reconstituted with Sodium Pertechnetate Tc 99m Injection and the resulting solution incubated in a boiling water bath for 15 minutes to form the drug substance, technetium Tc 99m apcitide, *in situ*. The drug product is produced using aseptic processing.

2.D.3.a. Composition and Dosage Form

Table 2.D.3-1 describes the composition used in the formulation of the drug product.

Table 2.D.3-1. Formulation Composition

Component	Quantity per vial (1 mL)[1]
Bibapcitide Trifluoroacetate	100 µg[2]
Sodium α-D-Glucoheptonate Dihydrate	75 mg
Tin Chloride Dihydrate	89 µg
Hydrochloric Acid	
Sodium Hydroxide	

The formulation is adjusted to pH 7.4 ± 0.1 with sodium hydroxide and/or hydrochloric acid prior to lyophilization. The headspace of the vial is back-filled with nitrogen in the

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