CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020887

Trade Name: ACUTECT FOR INJECTION, 100 ug PEPTIDE

Generic Name: KIT FOR THE PREPARATION OF TECNETIUM Tc 99m APCITIDE

Sponsor: DIATIDE, INC

Approval Date: 09/14/98

Indication(s): PROVIDES FOR SCINTIGRAPHIC IMAGING OF ACUTE VENOUS THROMBOSIS IN THE LOWER EXTREMITIES OF PATIENTS WHO HAVE SIGNS AND SYMPTOMS OF ACUTE VENOUS THROMBOSIS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020887

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020887

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-887

SEP 14 1998

Diatide, Inc.
9 Delta Drive
Londonderry, NH 03053

Attention: J. Kris Piper
Senior Director Regulatory Affairs and Quality Assurance

Dear Mr. Piper:

Please refer to your new drug application (NDA) dated August 19, 1997, received August 20, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcuTect™ (Kit for the Preparation of Technetium Tc 99m Apcitide) for injection, 100 ug peptide.

We acknowledge receipt of your submissions dated September 16, and 24, October 24, November 7, and 11, 1997; and January 6, 20, and 22, February 4, 11, 13, and 27, March 13, and 27, April 24, May 6, 22, and 28, June 17, and 26, July 2, and 21, August 10, 11, 14, and 28, 1998. Your submission of March 13, 1998 constituted a full response to our February 20, 1998 action letter. The user fee goal date for this application is September 16, 1998.

This new drug application provides for the use of AcuTect™ (Kit for the Preparation of Technetium Tc 99m Apcitide) for injection, 100 ug peptide, for scintigraphic imaging of acute venous thrombosis in the lower extremities of patients who have signs and symptoms of acute venous thrombosis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. The following additions to the vial and carton labels and package insert proposed in your August 14, 1998, letter are acceptable.

1. Include "Manufactured for Diatide, Inc., Londonderry, NH 03053 by Dr. Rentschler Biotechnolgie GmbH, Laupheim, Germany."

2. Include "Distributed by Diatide, Inc. and Nycomed Amersham."

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-887." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submissions dated March 13, and July 21, 1998. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Catalina Ferre-Hockensmith, Consumer Safety Officer, at (301) 443-3500.

Sincerely,

/S/

APPEARS THIS WAY
ON ORIGINAL

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020887

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-887

FEB 20 1998

Diatide, Inc.
9 Delta Drive
Londonderry, NH 03053

Attention: J. Kris Piper
Senior Director Regulatory Affairs and Quality Assurance

Dear Mr. Piper:

Please refer to your new drug application dated August 19, 1997, received August 20, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AcuTect™, (Kit for the Preparation of Technetium Tc 99m Apcitide), for injection, 100 ug peptide.

We acknowledge receipt of your submissions dated September 16, and 24, October 24, November 7, and 11, 1997; and January 6, 20, and 22, and February 4, and 11, 1998. The User Fee goal date for this application is February 20, 1998.

We have completed the review of this application as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following.

1. Submit the criteria for the Hamilton blinded reading of contrast venograms that were presented by your consultant, Dr. Ginsberg, at the February 9, 1998 Medical Imaging Advisory Committee (MIDAC) meeting.

2. Clarify the discrepancy in the amount of apcitide binding to the vitronectin receptors.

3. Submit patient narratives for the following laboratory changes that were above the upper limit of normal in study 280-33.

   Patient 20-1 for aminolevulinic acid and alanine aminotransferase; patient 5-2, 7-3, and 8-3 for gamma glutamyl transferase; patient 21-1 alanine aminotransferase and alkaline phosphatase; patient 10-1 alkaline phosphatase.

4. Submit revised draft labeling identical in content to the enclosed draft dated February 19, 1998.

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

In addition, we request that you commit to the following Phase 4 commitments.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. As appropriate, these new drop outs should be discussed.

3. Details of any significant changes or findings.

4. A summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling.

7. Information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events.

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

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

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

If you have any questions, please contact Catalina Ferre-Hockensmith, Consumer Safety Officer, at (301) 443-3500.

Sincerely yours,

/S/

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020887

FINAL PRINTED LABELING

September 14, 1998

Draft Package Insert

AcuTect™

Kit for the Preparation of Technetium Tc 99m Apcitide Injection.

DESCRIPTION

AcuTect™, Kit for the Preparation of Technetium Tc 99m Apcitide Injection, is intended for use in the preparation of technetium Tc 99m apcitide, a diagnostic radiopharmaceutical to be used by intravenous injection. Each vial contains a sterile, nonpyrogenic lyophilized mixture which is formulated with 100 µg of bibapcitide, 75 mg of sodium glucoheptonate dihydrate, 89 µg of stannous chloride dihydrate, and sufficient sodium hydroxide or hydrochloric acid to adjust the pH to 7.4 prior to lyophilization. The lyophilized powder is sealed under a nitrogen atmosphere with a rubber closure. The product does not contain an antimicrobial preservative.

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

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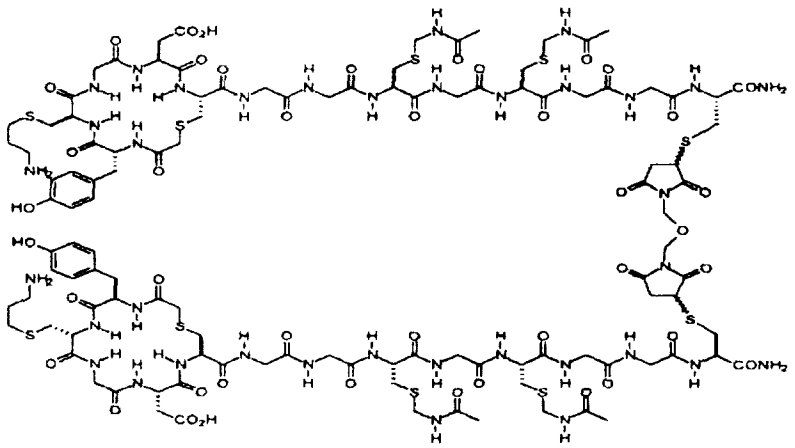
The structural formula of bibapcitide is:



Bibapcitide is composed of two apcitide monomers. When sterile, nonpyrogenic Sodium Pertechnetate Tc 99m Injection, in 0.9% Sodium Chloride Injection, U.S.P., is added to the vial and heated, the bibapcitide is split and forms a technetium-99m complex of apcitide. See "instructions for the preparation of technetium Tc 99m apcitide" below.

PHYSICAL CHARACTERISTICS

Technetium-99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] Photons that are useful for imaging studies are listed in Table 1.

Table 1.
Principal radiation emission data for Technetium-99m

Radiation	Mean Percent per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

External radiation

The specific gamma-ray constant for technetium-99m is 5.4 microcoulombs/ kg·MBq·hour (0.78 R/mCi·hour) at 1 cm. The first half-value thickness of lead for technetium-99m is 0.17 mm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of lead is shown in Table 2. For example, the use of a 0.25 cm thickness of lead will decrease the external radiation exposure by a factor of 1,000.

Table 2
Radiation attenuation by lead shielding

Lead Shield Thickness (cm)	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

[1] D.C. Kocher Radioactive Decay Tables, DOE/TIC - 11026. 108 (1981)

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals relative to the time of calibration are shown in Table 3.

Table 3.
Physical decay chart—Technetium-99m half-life 6.02 hours.

Hours	Fraction Remaining	Hours	Fraction Remaining
0	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

CLINICAL PHARMACOLOGY

GENERAL

Technetium Tc99m apcitide is a diagnostic radiopharmaceutical based upon a synthetic peptide that binds to the GPIIb/IIIa ($\alpha_2\beta_3$) adhesion-molecule receptors (of the integrin family) found on activated platelets. The peptide binds less avidly to the $\beta_3$chain of the vitronectin receptor found on endothelial cells.

PHARMACOKINETICS

Following a single intravenous dose of AcuTect™ containing 9.5-10.3 mCi of ^{99m}Tc technetium and 20.0-26.6 µg of bibapcitide in normal volunteers (n=10; 6 men and 4 women), the total radioactivity exhibited biexponential kinetics; the pharmacokinetic parameters (mean ± SD) are shown in table 4.

Table 4 Selected Pharmacokinetic Parameters in Normal Volunteers who Received AcuTect™			
Parameter	Values in All (N=10)	Male (N=6)	Female (N=4)
$T_{\frac{1}{2}}$ 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	0.10 ± 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

Following a single intravenous dose of AcuTect™ containing 13.9 - 21.2 mCi of ^{99m}Tc technetium and 65 - 90 µg of bibapcitide in 18 patients (14 men and 4 women) at risk of venous thrombosis (mean age ± SD is 53.5 ± 18 years; range 27-81), and two healthy female volunteers, the total radioactivity exhibited biexponential kinetics. The pharmacokinetics parameters (mean ± *SD*) are shown in table 5.

Table 5 Selected Pharmacokinetic Parameters in Patients* who Received AcuTect™			
Parameter	Values in All (N=20)	Male (N=14)	Female (N=6*)
$T_{\frac{1}{2}}$ 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

*Values included two healthy volunteers.

PROTEIN BINDING

In 16 patients (11 men and 5 women), the plasma protein binding (mean±SD) was 75.8±13.4% (with 75.5±15.4% in men and 76.3±8.7% in women). The *in vivo* plasma protein binding of total radioactivity in patients was determined by the centrifuge-assisted ultrafiltration method using the 30 min plasma sample.

External whole-body gamma scintigraphy showed highest localization of radioactivity in liver and kidney. (See Radiation Dosimetry section).

METABOLISM

Following a single intravenous AcuTect™ administration in patients and healthy volunteers at one-half hour after injection, a little less than two-thirds of the radioactivity circulating in plasma represented parent drug. This decreased to about 40% by six hours after injection. The percent of total radioactivity excreted as parent in urine mirrored plasma values, i.e., about 60% in the first hour after injection and decreasing to about 45% in the four- to six-hour postinjection interval.

One unidentified metabolite (Metabolite A), more polar than the parent drug, was detected in plasma. Two unidentified radioactive metabolites, both more polar than the parent drug, were observed in urine. One of the two metabolites, Metabolite A, was found in both plasma and urine. The other metabolite, Metabolite B, was first observed in the urine. Metabolite B was estimated at *< 30%* of total radioactivity while Metabolite A was estimated at *< 10%* of total radioactivity.

ELIMINATION

The overall biliary excretion (mean±SD) in 10 healthy volunteers at 22-24 hours following injection was 10.1 ± 2.5% of injected dose (ID). In men and women overall biliary excretion (mean±SD) was 9.6±3.2% ID (n=6) and 10.7±2.5%ID (n=4), respectively. Biliary excretion of radioactivity was estimated as the total amount of radioactivity in the gastrointestinal tract and gallbladder determined by scintigraphic imaging.

Half of the injected dose of radioactivity appeared in urine at two hours after injection and three-quarters by 8 hours. Nearly 80% of the injected dose of radioactivity underwent urinary excretion during the first day. The amount of total radioactivity (mean±SD) ultimately eliminated in urine was 79.5±5.8%ID in 10 healthy volunteers. In men and women, respectively, the results were 78.5±7.4%ID (n=6) and 81.0±2.2%ID (n=4) respectively. In 9 patients, the result was 56.7±13.4%ID.

SPECIAL POPULATIONS

Elderly Population: In a clinical study evaluating AcuTect™ in six elderly patients (age range = 70-81 years) and 12 patients under 65 years old (age range = 27-64 years) the disposition of radioactivity appeared to be similar.

Gender Effect: Significant differences in the disposition of radioactivity were not seen between men and women.

Pediatrics: The pharmacokinetics of AcuTect™ in neonates, children and adolescents below the age of 16 years have not been studied.

Renal Insufficiency: Radioactivity studies of AcuTect™ disposition have not been conducted in patients with renal disease.

Hepatic Insufficiency: Radioactivity studies of AcuTect™ disposition have not been conducted in patients with hepatic disease.

Pharmacodynamics

In vitro and *in vivo* studies in laboratory animals suggest that the apcitide binding to GPIIb/IIIa receptor requires platelet activation before binding can occur. In acute venous thrombosis, after anticoagulant therapy has begun, the duration of receptor site availability for apcitide binding has not been studied. Based on in vivo and ex vivo animal data, AcuTect™ appears to detect acute and not chronic venous thrombosis. This has not been confirmed in human clinical studies. Platelet aggregation studies showed that peptide components in the injection inhibit adenosine diphosphate induced platelet aggregation at concentrations higher than those proposed for human use. A dose range in which the effect is not seen has not been determined. The effect on bleeding time was not studied.

DRUG-DRUG INTERACTIONS

Drug-drug interaction studies have not been conducted with AcuTect. The effect of drugs that increase or decrease prothrombin time on the binding of AcuTect to activated platelets has not been studied.

The effect of heparin, warfarin, or aspirin on apcitide binding has not been studied in humans. In animal *in vitro* and *ex vivo* models, heparin or aspirin did not change the inhibition of platelet aggregation caused by apcitide. Whether heparin or aspirin change the ability of apcitide to bind to GPIIb/IIIa receptors on activated platelets was not studied. The effect of the duration of anticoagulation on apcitide binding was not studied.

CLINICAL STUDIES

AcuTect™ was studied in two open-label, multicenter clinical studies in a total of 280 patients (135 in study A, 145 in study B) with signs and symptoms of suspected acute venous thrombosis of the lower extremity(ies). At enrollment of the patients, the following signs and symptoms were reported: pain/tenderness (86%), swelling (83%), increased warmth (41%), erythema (38%), and palpable cord (8%). Age, gender, racial and ethnic groupings were: 48% men and 52% women, mean age of 60 years (range: 17 to 88 years), 91% Caucasian, 3% Black, and 6% of other ethnicity. Approximately 24% of the patients had a history of either deep venous thrombosis or pulmonary embolus.

All 280 patients had scintigraphic imaging with AcuTect™ 480 to 1,100 Mbq (13 to 30 mCi) and an iodinated contrast-enhanced venography. All imaging was completed within 36 hours of study enrollment. Thirty-seven patients were ineligible for evaluation because of protocol violations or incomplete image sets. Of the remaining 243 patients, 236 (85%) had images that were evaluable by both AcuTect™ and contrast venography.

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AcuTect™ images were obtained at 10, 60, and 120-180 minutes after injection of AcuTect™. The images for each study were independently evaluated by three nuclear medicine physicians who were blinded to all other clinical study data. Evaluations were performed based on the times that AcuTect™ images were obtained from each patient. Images were scored as "positive" for acute venous thrombosis if the deep veins demonstrated both asymmetric uptake between the two lower extremities (with or without superimposed diffuse uptake) in contrast enhanced images, and asymmetry in both anterior and posterior projections. Additionally, if the asymmetry appeared only after extreme contrast enhancement, then diffuse asymmetry must be present for scoring an image as positive. Information regarding AcuTect™ images that did not meet the criteria for acute venous thrombosis was not collected.

Contrast venography images were read twice. The first contrast venography reading was a prospectively planned reading by three independent radiologists from different centers who were blinded to the all other clinical study data. Criteria for this reading were not established by protocol. The second contrast venography reading was retrospectively performed by three radiologists at one research center who were blinded to the all other clinical study data. The criteria used for this reading of contrast venography images included the assessment of deep veins in the proximal (iliac, common femoral, superficial femoral, deep femoral and popliteal veins) and distal (calf, peroneal, posterior tibial, and anterior tibial veins, up to and including the point of trifurcation of the calf vein) regions. Images were interpreted as follows, a) intraluminal filling defect (positive for venous thrombosis), b) no filling defect - all veins visualized (negative for venous thrombosis), or c) inadequate. The primary efficacy variable was the agreement between the blindly read AcuTect™ and the blindly read research center contrast venography (e.g., positive or negative diagnosis by both AcuTect™ and contrast venography).

Overall, in the blinded AcuTect™ reading of Study A and B respectively, the percent of AcuTect™ images that were interpreted as positive for acute venous thrombosis is 54 (48%) and 41 (33%). The diagnostic results of the two blinded contrast venography readings depended upon the method. The blinded contrast venography reading without protocol established criteria resulted in 51 (45%) and 101 (82%) of patients considered as positive in Study A and B respectively. The research center reading of venography with uniform criteria resulted in 24 (21%) and 40 (33%) of the patients considered as positive. Table 6 shows the positive, and negative results of acute venous thrombosis made by AcuTect™ and the contrast venography reading with the research center criteria. Differences in sample size are noted in footnotes to the table.

Table 6

Diagnosis of Acute Venous Thrombosis (AVT) Comparing AcuTect™ Blinded Reading with Contrast Venography (CV) Blinded Reading using the Research Center Criteria

		Positive AVT (AcuTect™[1])	Negative AVT (AcuTect™[1])
Study A (N=113)[2]	Positive AVT (CV)	20 (18%)	4 (4%)
	Negative AVT (CV)	34 (31%)	52 (47%)
Study B (N = 123)[2]	Positive AVT (CV)	21 (17%)	19 (16%)
	Negative AVT (CV)	20 (17%)	60 (50%)

[1] AcuTect™ data are from the majority of the blinded readers for each study.
[2] In Study A, results from 3 patients were indeterminate either by AcuTect™ or by the research center CV.
In Study B, results from three patients were indeterminate by the research center CV.
Percents are based on 110 and 120 evaluable patients in study A and B, respectively.

Table 7 shows the range of overall agreement rates for AcuTect™ images compared to the Research Center Uniform Criteria Blinded Read of the contrast venography. Although the agreement rate was statistically similar for all AcuTect™ imaging time points, there was a trend toward stronger agreement rates if the AcuTect™ images were obtained at 10 and 60 minutes after injection.

Table 7

Agreement[a] Rates between AcuTect™ and the Research Center Criteria Blinded Reading Contrast Venography (CV)

Study	AcuTect™ vs. Research Center Blind CV
280-32A (N=113)[b]	56-71%
280-32B (N=123)[b]	66-73%

[a] Range for the blinded readers.
[b] Evaluable patients.

The differences in the AcuTect™ interpretations and contrast venography diagnoses were not evaluated in clinical follow-up of patients. How negative AcuTect™ images should be used in the diagnostic evaluation or therapeutic management of patients with suspected acute venous thrombosis has not been studied.

The safety of more than one dose of AcuTect™ in the diagnostic evaluation of patients has not been studied.

INDICATIONS AND USAGE

AcuTect™ is indicated for scintigraphic imaging of acute venous thrombosis in the lower extremities of patients who have signs and symptoms of acute venous thrombosis.

CONTRAINDICATIONS

None known.

WARNINGS

Clinical follow-up studies of patients with negative AcuTect™ scans have not been performed to determine if negative image findings mean the absence of acute venous thrombosis. If a patient has clinical signs and symptoms of acute venous thrombosis, a clinical management decision to withhold treatment with anticoagulants should not be based on a negative AcuTect™ study alone.

After administration of AcuTect™, as with the administration of other intravenous drugs, patients with history of drug reactions, other allergies, or immune system disorders should be observed for several hours. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating anaphylactic reactions should be available. (See adverse reactions section).

PRECAUTIONS

General

The contents of AcuTect™ Kit are intended only for use in the preparation of technetium Tc 99m apcitide, and are not to be administered to the patient without reconstitution.

Hypersensitivity: Small peptides may be immunogenic. Of 642 patients observed for 3 hours after AcuTect™ injection and of whom 169 were monitored for 24 hours, one patient had acute hypotension that began within 10 minutes of injection and, over 60 minutes, progressed to a systolic pressure of 70 mmHg.

In preliminary studies of IgG binding to apcitide by ELISA assay, IgG binding was not detected. Other measures of immune function (e.g., complement, immune complexes, lymphokines) have not been studied. In preclinical animal models, there was a reduction in the absolute or relative weight of the spleen. The clinical significance of the reduced splenic weight to immune function is not known.

Technetium Tc 99m apcitide, like other radioactive drugs, must be handled with care and appropriate safety measures should be taken to minimize radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to the patient consistent with appropriate patient management.

Radiopharmaceutical agents should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

Urinary excretion of radioactivity occurs over about 24 hours (with 75% occurring during the first 8 hours). Special precautions, such as bladder catherization, should be taken with incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen, and the patient's environment. Studies have not been done to evaluate the need to adjust the dose of AcuTect™ in patients with renal impairment.

INFORMATION FOR PATIENTS

To minimize the absorbed radiation dose to the bladder, adequate hydration should be encouraged to ensure frequent voiding during the first few hours after AcuTect™ injection. To help protect themselves and others in their environment, patients need to take the following precautions for 12 hours following injection. Whenever possible, a toilet should be used, rather than a urinal, and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely. Patients should wash their hands thoroughly after each voiding. If blood or urine gets onto clothing, the clothing should be washed separately

LABORATORY TESTS

AcuTect™ has been shown to inhibit platelet aggregation (see clinical pharmacology section). The effect of AcuTect™ on bleeding time in humans has not been studied.

Moderate elevations in liver enzymes were noted in rare cases at three hours and persisted to at least 24 hours following administration of AcuTect™.

DRUG INTERACTIONS

Clinically detectable drug interactions were not seen or explicitly studied in patients who received technetium Tc 99m apcitide and other concomitant medications. For potential anticoagulant interactions, see the Clinical Pharmacology section.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies have not been conducted to evaluate carcinogenic potential or effects on fertility.

AcuTect™ was not mutagenic in the Ames Test or mouse lymphoma test, and it was not clastogenic in the mouse micornucleus test.

PREGNANCY

Pregnancy Category C. Animal reproduction studies have not been conducted with technetium Tc 99m apcitide. It is not known whether technetium Tc 99m apcitide or the other peptide components of the formulation can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Technetium Tc 99m apcitide should be given to a pregnant woman only if clearly needed. Studies in pregnant women have not been conducted.

NURSING MOTHERS

Technetium Tc 99m pertechnetate is excreted in human milk. It is not known whether technetium Tc 99m apcitide is excreted in human milk. Caution should be exercised when technetium Tc 99m apcitide is administered to nursing women. Wherever possible, infant formula should be substituted for breast milk until the technetium has been eliminated.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse events were evaluated in clinical studies of 642 adults who received technetium Tc 99m 20.0 mCi labeled to approximately 70 - 100 µg of bibapcitide. Of these adults, 46% were women and 54% men. The mean age was 57.0 years (17 to 95 years). In all patients, adverse events were monitored for at least 3 hours. In a subset of 169 patients, adverse events were monitored for 24 hours.

Deaths did not occur during the clinical study period. Following injection of technetium Tc 99m apcitide, a serious episode of hypotension occurred in one patient who had acute hypotension that began within 10 minutes of injection and, over 60 minutes, progressed to a systolic pressure of 70 mmHg.

At least one adverse event occurred in 29/642 (4.5%) of patients after technetium Tc 99m apcitide injection. Pain was the most commonly reported adverse event (1.7% of patients or healthy volunteers). Table 8 lists adverse events reported in 0.5% or more of patients who received technetium Tc 99m apcitide.

Table 8 ADVERSE EVENTS REPORTED IN ≥0.5 % OF PATIENTS FOLLOWING AcuTect™ INJECTION IN CLINICAL STUDIES	
Number of Patients Exposed to AcuTect™	642
Number of Patients with At Least One Adverse Event	29 (4.5%)
Body As a Whole	21 (3.3%)
Pain (back, leg, chest)	11 (1.7%)
Headache	5 (0.8%)
Cardiovascular System	13 (2.0%)
Hypotension	5 (0.8%)
Hypertension	3 (0.5%)

Other adverse events which occurred in < 0.5% of patients following receipt of AcuTect™ included: agitation, asthenia, bradycardia, cardiovascular disorder, chills, convulsions, dizziness, fever, hypertonia, injection site reaction, liver enzyme elevation, nausea, pallor, paresthesia, pruritus, sweat, tachycardia, twitch, urticaria, and vomiting.

OVERDOSAGE

Clinical consequences of overdosage with technetium Tc 99m apcitide have not been studied.

DOSAGE AND ADMINISTRATION

To detect acute venous thrombosis in a lower extremity, reconstituted AcuTect™ should be administered as a peripheral intravenous injection in an upper extremity, at a dose of approximately 100 µg of bibapcitide radiolabeled with 20 mCi of technetium 99m.

Technetium Tc 99m apcitide should be drawn into the syringe and administered using sterile technique. If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. Unused portions of the drug must be discarded appropriately. (See Instructions for Preparation Section).

Lower Extremity Imaging

AcuTect™ imaging should begin between 10 and 60 minutes after injection.

Patients should void just before imaging in order to limit the influence of urinary bladder radioactivity since technetium Tc 99m apcitide is cleared from the blood by the kidneys. If it is determined that imaging needs to be repeated, additional images may be obtained up to 180 minutes without reinjection. The safety of more than one dose has not been studied. (See Clinical Pharmacology section and Precautions, General).

Positive AcuTect™ uptake in the deep venous structures is defined as asymmetric vascular uptake (with or without superimposed diffuse uptake) in contrast enhanced images, and asymmetry in both anterior and posterior projections. If asymmetry appears only after extreme contrast enhancement, then diffuse asymmetry must also be present for scoring an image as positive.

Superficial increased uptake is not to be interpreted as acute deep venous thrombosis.

RADIATION DOSIMETRY

Based on human data, the absorbed radiation doses to an average adult (70 kg) from an intravenous injection of technetium Tc 99m apcitide are listed in Table 9. The values are listed in descending order as rad/mCi and mGy/MBq and assume urinary bladder emptying at 4.8 hours.

Table 9
Radiation Absorbed Doses for a 70kg Adult

Target Organ	rad/mCi	mGy/MBq
Urinary Bladder Wall	0.22	0.060
Kidneys	0.050	0.014
Upper Large Intestine Wall	0.039	0.010
Lower Large Intestine Wall	0.037	0.010
Uterus	0.034	0.0092
Thyroid Gland	0.022	0.0060
Testes/Ovaries	0.020/0.023	0.0053/0.0063
Lungs	0.016	0.0043
Red Marrow	0.0091	0.0025
Breasts	0.0050	0.0013

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, 1-4, 1988) and gave a value of 0.0093mSv/MBq (0.0034 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.

The doses should be measured immediately before administration by a suitable radioactivity calibration system, such as a radioisotope dose calibrator. The dose of radioactivity to be administered and the patient should be verified before injecting technetium Tc 99m apcitide.

1. Prepare a rolling-boil water bath containing a lead vial shield standing in and equilibrated with the boiling water bath.
2. Allow the vial to warm to room temperature (20 to 25° C) and place it in a suitable shielding container, remove the flip-off top and sanitize the rubber septum with sanitizing alcohol swab .
3. Using a shielded syringe, inject the required activity of up to 50 mCi (1.8 GBq) of Sodium Pertechnetate Tc 99m Injection, (diluted as appropriate with 0.9% Sodium Chloride Injection, U.S.P.) into the shielded vial See Cautionary Notes 1 and 2. Before removing the syringe from the vial, withdraw a volume of gas from the vial equal to the volume of pertechnetate added in order to normalize the pressure inside the vial. Swirl the vial gently for 10 seconds in order to ensure complete dissolution of the powder.
4. Immediately transfer the reaction vial to the lead shield in the boiling water bath, maintaining the vial in an upright position for 15 minutes. Allow the vial to cool for 10 to 15 minutes before proceeding.
5. Assay the total radioactivity, complete the user radiation label and attach it to the vial.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Visually inspect the reconstituted solution at a safe distance through leaded glass. Do not use if it is not clear or if it contains foreign particulate matter.
7. Store the reconstituted injection at room temperature 20-25 °C (68 to 77° F), and use within six hours of preparation.

Cautionary Notes.

1. The volume of diluted Sodium Pertechnetate Tc 99m Injection, added to the vial must be in the range of one to three milliliters.
2. The radioactive concentration of the diluted generator eluate must not exceed 50 mCi/mL (1 8 GBq/ml) when it is added to the vial.
3. After the addition of Sodium Pertechnetate Tc 99m Injection, adequate shielding of the final preparation must be maintained.
4. **The labeling reaction involved in the preparation of technetium Tc 99m apcitide depends upon maintaining tin in the divalent (reduced) state. Any oxidant present in the Sodium Pertechnetate Tc 99m Injection, might adversely affect the quality of the preparation. Do not use Sodium Pertechnetate Tc 99m Injection, that contains oxidants for the preparation of the labeled product.**

5. 0.9% Sodium Chloride Injection, U.S.P., must be used as the diluent for pertechnetate. **Do not use bacteriostatic sodium chloride as a diluent for pertechnetate, because it might adversely affect the radiochemical purity and, hence, *the biological distribution of the tracer.***
6. The contents of the AcuTect™ vial are sterile and nonpyrogenic. The vial contains no bacteriostatic preservative. It is essential that the user follow the directions carefully and adhere to aseptic procedures during the preparation of the radiopharmaceutical.

Quality control

An assay of the radiochemical purity of the prepared injection can be performed using the following chromatographic procedures.

Equipment and Materials

1. Two Gelman ITLC-SG strips (2 cm x 10 cm)
2. Two developing jars and covers
3. Saturated sodium chloride solution[2] (SAS)
4. Distilled water, or its equivalent, e.g., Water for Injection, U.S.P. (Water).
5. One 1-cc syringe and 21-gauge needle
6. Suitable counting equipment

Method

1. Pour the distilled water and SAS into separate developing jars to a depth of approximately 0.5 cm. Cover the jars and allow to equilibrate with the solvent vapors.
2. Mark two Gelman ITLC-SG strips with a light pencil at 1 cm from the bottoms of each.
3. Spot one drop (approximately 10 microliters) of technetium Tc 99m apcitide injection at the origin of each strip using the hypodermic needle. Do not allow the spots to dry. CAUTION: Do not allow the needle to touch the strip.
4. Place the developing jars behind a lead shield.
5. Place one ITLC-SG strip in the distilled water as the developing solvent. Place the second ITLC-SG strip in the SAS developing solvent. Place the strips upright in the respective developing solvent such that the spot is above the solvent line and the top of the strip leans against the side of the jar. CAUTION: Do not allow the sides of the strip to contact the side of the jar. Cap the developing jars.
6. Allow the solvent front to move to the top of the strip.

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[2] May be prepared by adding about five grams of sodium chloride to the bottom of one chromatography chamber; add approximately 5 to 10 milliliters of distilled water to the solid sodium chloride and shake periodically during 10 to 15 minutes. Solid sodium chloride should remain at the bottom of the jar; if there is no residue, add more solid sodium chloride and shake again for 10 to 15 minutes. Continue until a solid residue remains. (The Saturated Sodium Chloride Solution can be reused. Add more distilled water or sodium chloride as needed for subsequent use, always maintaining some solid undissolved sodium chloride at the bottom of the chamber.)

7. Remove the strips from the jars and allow the strips to dry behind a lead shield.
8. Cut the strips as described below:
   a. ITLC-SG Water: cut the strip at Rf 0.25 (25% of the distance from the origin to the solvent front)
   b. ITLC-SG SAS: cut the strip at Rf 0.75 (75% of the distance from the origin to the solvent front)

   Count each strip section in a dose calibrator and interpret the results as follows:

Percent Technetium-99m immobile material = A

$$A = 100 \times \frac{\textit{Activity in bottom piece of ITLC - SG Water Strip (Rf 0-0.25)}}{\textit{Total Activity in both pieces of ITLC - SG Water Strip}}$$

Percent Technetium-99m pertechnetate and Technetium-99m labeled glucoheptonate = B

$$B = 100 \times \frac{\textit{Activity in top piece of ITLC-SG SAS Strip (Rf 0.75-1.0)}}{\textit{Total Activity in both pieces of ITLC-SG SAS Strip}}$$

Percent Technetium Tc 99m Apcitide = 100 - (A + B). A value of at least 90% should be obtained in a satisfactory preparation.

HOW SUPPLIED

Each kit contains one vial containing a sterile, nonpyrogenic, freeze-dried mixture of bibapcitde, stannous chloride dihydrate and sodium glucoheptonate dihydrate, together with a package insert and, adverse event reporting cards. Kits are available in packs of 5 vials.

Storage

Store the kit in a refrigerator at 2 to 8° C, (36 to 46° F). Store the reconstituted injection solution at 20-25 °C (68 to 77° F), using appropriate radiation shielding, for up to 6 hours.

The kit should be protected from light.

This reagent kit is approved for distribution to persons licensed by the U.S. Nuclear Regulatory Commission to use byproduct material identified in §35.200, or under an equivalent license of an Agreement State.

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Rx only.

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