

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020887

CHEMISTRY REVIEW(S)

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-887

DATE REVIEWED: August 12, 1998

REVIEW #: Review # 5 (Labeling)

REVIEWER: Ravi S. Harapanhalli, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NC (Vial and Carton)	10-AUG-98	10-AUG-98	10-AUG-98
NC (Letter of Clarification)	11-AUG-98	11-AUG-98	11-AUG-98

NAME & ADDRESS OF APPLICANT: DIATIDE INC.,
9 Delta Drive
Londonderry, NH 03053

DRUG PRODUCT NAME

Proprietary: Peptide P280, ACUTECT™, (Kit for the preparation of Technetium 99m Apcitide)

Established (USAN):

Bibapcitide

Code Name/#:

P280

Chem.Type/Ther.Class:

Diagnostic Radiopharmaceutical

PHARMACOL. CATEGORY/INDICATION:

Diagnostic radiopharmaceutical for detection and localization of acute venous thrombosis.

DOSAGE FORM:

Sterile solution

STRENGTHS:

100µg P280/20 mCi Tc99m in 1-3 ml saline

ROUTE OF ADMINISTRATION:

Intravenous

Rx/OTC:

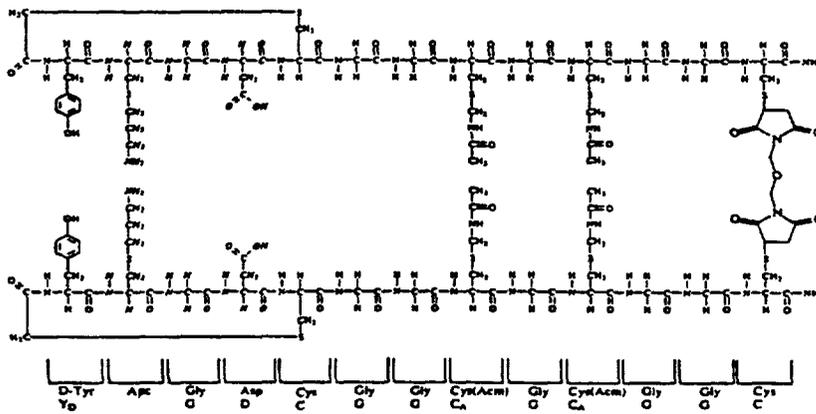
Rx OTC

SPECIAL PRODUCTS:

Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: C₁₁₂H₁₆₂N₃₆O₄₃S₁₀; **molecular Weight:** 3021.4



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 \rightarrow 5), (1' \rightarrow 5'),-bis(sulfide).

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: None

REMARKS: The label for vial and carton, submitted by the sponsor on August 10, 1998 via fax, was reviewed and found to be deficient in a few statements. A letter of clarification from the sponsor submitted on August 11, 1998 was also reviewed.

CONCLUSIONS & RECOMMENDATIONS: The Labeling for vial, carton and package insert, were reviewed from CMC perspective and appropriate deficiencies are pointed out. Sponsor may make changes in their labeling accordingly.

/S/

Ravi S. Harapanhalli, Ph.D.
Review Chemist

APPEARS THIS WAY
ON ORIGINAL

cc:
Org. NDA 20887
HFD-160/Division File
HFD-160/Chemist/Harapanhalli/07/01/98
HFD-160/PM/Ferre-Hockensmith
HFD-160/TEAMLEADER/Leutzinger
HFD-820/DIVISION DIRECTOR/Gibbs
R/D Init by: TEAMLEADER

/S/

3/13/98

filename: C:/mydocuments/NDA20887f

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

NDA #: 20-887

DATE REVIEWED: July 29, 1998

REVIEW #: Review # 4

REVIEWER: Ravi S. Harapanhalli, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	19-AUG-97	20-AUG-97	27-AUG-97
AMENDMENT (BC)	11-FEB-98	12-FEB-98	13-FEB-98
AMENDMENT (NC)	11-FEB-98	11-FEB-98	13-APR-98
AMENDMENT (AZ)	13-MAR-98	16-MAR-98	13-APR-98
AMENDMENT (BC)	02-JUL-98	06-JUL-98	07-JUL-98

NAME & ADDRESS OF APPLICANT:

DIATIDE INC.,
 9 Delta Drive
 Londonderry, NH 03053

DRUG PRODUCT NAME

Proprietary: Peptide P280, ACUTECT™, (Kit for the preparation of Technetium 99m Apcitide)
Established (USAN): Bibapcitide
Code Name/#: P280
Chem.Type/Ther.Class: Diagnostic Radiopharmaceutical

PHARMACOL. CATEGORY/INDICATION:

Diagnostic radiopharmaceutical for detection and localization of acute venous thrombosis.

DOSAGE FORM:

Sterile solution

STRENGTHS:

100µg P280/20 mCi Tc99m in 1-3 ml saline

ROUTE OF ADMINISTRATION:

Intravenous

Rx/OTC:

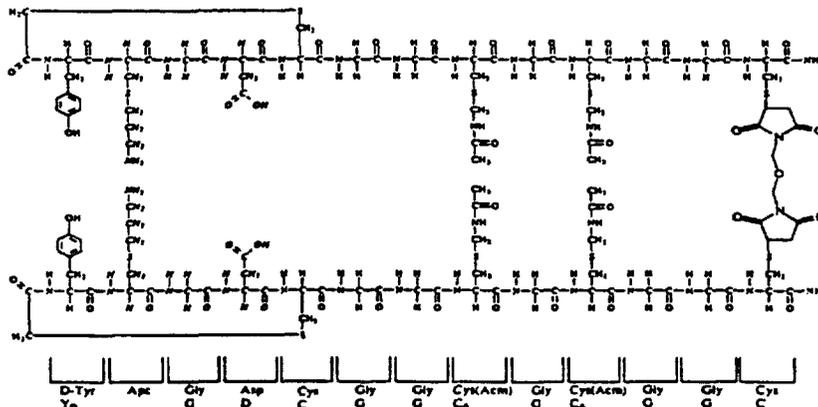
Rx OTC

SPECIAL PRODUCTS:

Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: C₁₁₂H₁₆₂N₃₆O₄₃S₁₀; **molecular Weight:** 3021.4



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

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: None

CONCLUSIONS & RECOMMENDATIONS: All outstanding CMC issues in the NDA have been addressed by the sponsor. The cGMP inspections of the manufacturing site and the contract laboratories are satisfactory. From the CMC stand point, the NDA is recommended for an approval.

**APPEARS THIS WAY
ON ORIGINAL**

/S/

7/29/98

Ravi S. Harapanhalli, Ph.D.
Review Chemist

cc:
Org. NDA 20887
HFD-160/Division File
HFD-160/Chemist/Harapanhalli/07/01/98
HFD-160/PM/Ferre-Hockensmith
HFD-160/TEAMLEADER/Leutzinger
HFD-820/DIVISION DIRECTOR/Gibbs
R/D Init by: TEAMLEADER

/S/

7/30/98

filename: C:/mydocuments/NDA20887e

JUL 1 1998

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

NDA #: 20-887

DATE REVIEWED: July 01, 1998

REVIEW #: Ammended review # 3

REVIEWER: Ravi S. Harapanhalli, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	19-AUG-97	20-AUG-97	27-AUG-97
AMENDMENT (BC)	11-FEB-98	12-FEB-98	13-FEB-98
AMENDMENT (NC)	11-FEB-98	11-FEB-98	13-APR-98
AMENDMENT (AZ)	13-MAR-98	16-MAR-98	13-APR-98

NAME & ADDRESS OF APPLICANT:

DIATIDE INC.,
9 Delta Drive
Londonderry, NH 03053

DRUG PRODUCT NAME

Proprietary: Peptide P280, ACUTECT™, (Kit for the preparation of Technetium 99m Apcitide)

Established (USAN): Bibapcitide

Code Name/#: P280

Chem. Type/Ther. Class: **Diagnostic Radiopharmaceutical**

PHARMACOL. CATEGORY/INDICATION:

Diagnostic radiopharmaceutical for detection and localization of acute venous thrombosis.

DOSAGE FORM:

Sterile solution

STRENGTHS:

100µg P280/20 mCi Tc99m in 1-3 ml saline

ROUTE OF ADMINISTRATION:

Intravenous

Rx/OTC:

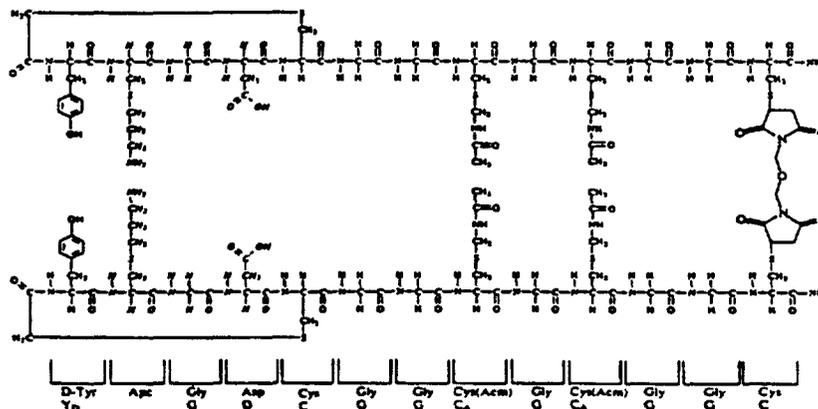
Rx OTC

SPECIAL PRODUCTS:

Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: C₁₁₂H₁₆₂N₃₆O₄₃S₁₀; molecular Weight: 3021.4



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

NDA #: 20-887

DATE REVIEWED: June 01, 1998

REVIEW #: 3

REVIEWER: Ravi S. Harapanhalli, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
RESPONSE (NC)	11-FEB-98	11-FEB-98	13-APR-98
RESPONSE (AZ)	13-MAR-98	16-MAR-98	13-APR-98

NAME & ADDRESS OF APPLICANT:
DIATIDE INC.,
9 Delta Drive
Londonderry, NH 03053

DRUG PRODUCT NAME

Proprietary: Peptide P280, ACUTECT™, (Kit for the preparation of Technetium 99m Apcitide)
Established (USAN): Bibacpitide
Code Name/#: P280
Chem.Type/Ther.Class: Diagnostic Radiopharmaceutical

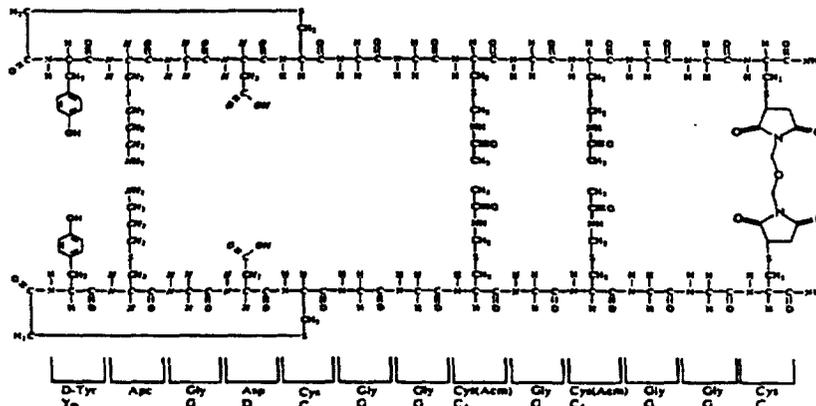
PHARMACOL. CATEGORY/INDICATION: Diagnostic radiopharmaceutical for detection and localization of acute venous thrombosis.

DOSAGE FORM: Sterile solution
STRENGTHS: 100 µg P280/20 mCi Tc 99m in 1-3 ml Saline
ROUTE OF ADMINISTRATION: Intravenous
Rx/OTC: Rx OTC
SPECIAL PRODUCTS: Yes No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: C₁₁₂H₁₆₂N₃₆O₄₃S₁₀; **molecular Weight:** 3021.4



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 \rightarrow 5), (1' \rightarrow 5'),-bis(sulfide).

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

APPEARS THIS WAY
ON ORIGINAL

CONSULTS: None

REMARKS:

The NDA was subsequently transferred to me and I have reviewed the documents NC, dated February 11, 1998, and AZ (dated March 13, 1998)

Two outstanding issues are:

1. Satisfactory cGMP re-inspection of facility following a 483 recommendation to withhold approval application dated February 4, 1998.
2. Approval of Methods Validation package by the FDA field laboratories.

CONCLUSIONS & RECOMMENDATIONS:

From the standpoint of chemistry, NDA 20,887 is recommended for approval subject to satisfactory re-inspection of facility following a 483 dated February 4, 1998

/S/

APPEARS THIS WAY
ON ORIGINAL

Ravi S. Harapanhalli, Ph.D.
June 01, 1998

cc:
Org. NDA # 20887
HFD-160/Division File
HFD-160/Chemist/Harapanhalli/05/26/98
HFD-160/CSO/Ferre-Hockensmith
HFD-160/TEAMLEADER/Leutzinger
HFD-820/DNDCII/Gibbs
R/D Init by: TEAMLEADER

/S/

6/4/98

APPEARS THIS WAY
ON ORIGINAL

filename: C:/mydocuments/NDA20887

**DIVISION OF NEW DRUG CHEMISTRY-II (DMIRDP, HFD-160)
Review of Chemistry, Manufacturing, and Controls****NDA #: 20-887****CHEM.REVIEW #: 2****REVIEW DATE: 02-13-98****SUBMISSION/TYPE:****DOCUMENT DATE:****CDER DATE:****ASS.DATE:**

ORIGINAL

08-19-97

08-20-97

08-27-97

Amendment (NC)

02-11-98

02-12-98

02-12-98

NAME & ADDRESS OF APPLICANT:

Diatide, Inc., 9 Delta Drive

Londonderry, NH 03053

Contact Name: J. Kris Piper

Tel..(603) 437 8970; Fax...(603) 437 8977

DRUG PRODUCT NAME:

Proprietary:

Peptide P280, ACUTECT™, (Kit for the
Preparation of ^{99m}Tc Apcitide)

Nonproprietary/USAN:

Bibapcitide; Code Names/#'s:P280

Chem Abstract #:

[153507-46-1]; CFN Number: [20 24023]

Chemical Type/Therapeutic Class: Diagnostic Radiopharmaceutical

ANDA SUITABILITY PETITION/DESI/PATENT STATUS: Not Applicable**PHARMACOLOGICAL CATEGORY/INDICATION: Diagnostic radiopharmaceutical for
detection and localization of acute venous thrombosis.**

Dosage Form:

Sterile Solution

Strengths:

100 µg P280/20 mCi ^{99m}Tc/1-3 mL Saline

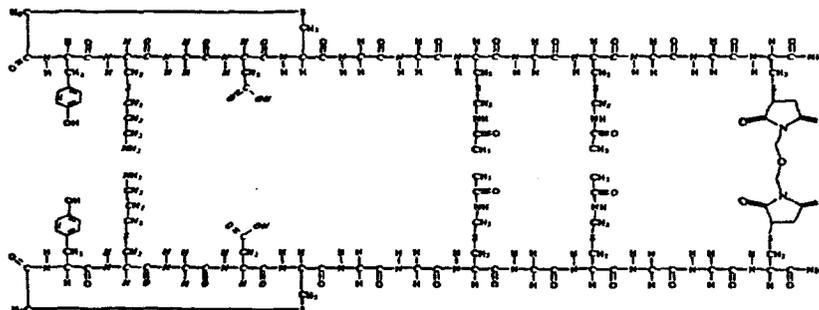
Route of Administration:

Intravenous

Dispensed:

 Rx OTC**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:**

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).

Molecular Formula: C₁₁₂H₁₆₂N₃₆O₄₃S₁₀; Molecular Weight: 3021.4

RELATED DOCUMENTS: None

CONSULTS: None.

REMARKS/COMMENTS:

The latest submission (NDA 20,887 NC) contained responses to all chemistry issues from original review of the NDA. The responses were found to be adequate. A few clarification issues have been resolved by teleconference with the sponsor

Other outstanding non-CMC issues are:

1. Current Good Manufacturing Practice (cGMP) Inspection of Diatide and contract labs. Requests for cGMP inspection were filed by EER on 9/11/97. Status as of 02/12/98: OC is currently withholding cGMP approval of facilities and has not concluded inspection of those of
2. Trademark approval. The request for trademark review of the name "AcuTect™" was filed on 9/27/97. Status as of 02/12/98: final evaluation on trademark request by the Labeling & Nomenclature committee (chair; Dr. Dan Boring) is not yet known.

CONCLUSION & RECOMMENDATIONS:

From the standpoint of chemistry, NDA 20,887 is recommended for approval subject to satisfactory cGMP inspections and trademark request evaluation by the Agency.

IS/
2/13/98

Qaisy Salako, Ph.D.
Review Chemist

IS/
2/13/98

CC:Orig. NDA #20,887
HFD-160/Division File
HFD-160/Medical Officer/Zolman; HFD-160/Chemist/Salako
HFD-160/Toxicologist/Laniyonu; HFD-160/Pharmacokineticist/Udoh
HFD-160/CSO/Ferre-Hockensmith
HFD-160/Chemistry Team Leader/Leutzinger
HFD-820/DNDCII/Gibbs

DIVISION OF NEW DRUG CHEMISTRY-II (DMIRDP, HFD-160)
Review of Chemistry, Manufacturing, and Controls

<u>NDA #:</u> 20-887	<u>CHEM.REVIEW #:</u> 1	<u>REVIEW DATE:</u> 12-04-97	
<u>SUBMISSION/TYPE:</u>	<u>DOCUMENT DATE:</u>	<u>CDER DATE:</u>	<u>ASS.DATE:</u>
ORIGINAL	08-19-97	08-20-97	08-27-97

NAME & ADDRESS OF APPLICANT:

Diatide, Inc., 9 Delta Drive
Londonderry, NH 03053
Contact Name: J. Kris Piper Tel..(603) 437 8970; Fax...(603) 437 8977

DRUG PRODUCT NAME:

Proprietary:	Peptide P280, ACUTECT™, (Kit for the Preparation of ^{99m} Tc Apcitide)
Nonproprietary/USAN:	Bibapcitide; Code Names/#'s:P280
Chem Abstract #:	[153507-46-1]; CFN Number: [20 24023]
Chemical Type/Therapeutic Class:	Diagnostic Radiopharmaceutical

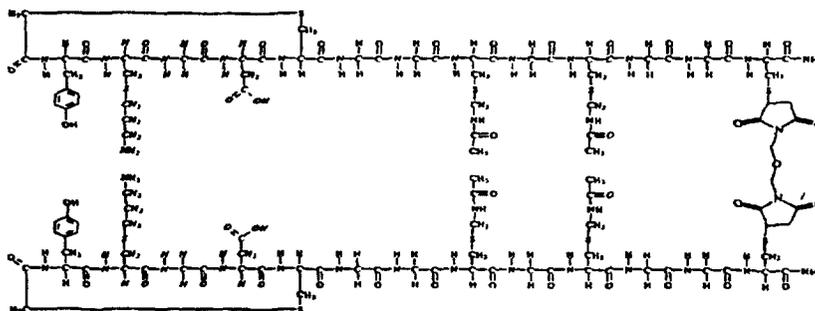
ANDA SUITABILITY PETITION/DESI/PATENT STATUS: Not Applicable**PHARMACOLOGICAL CATEGORY/INDICATION:** Diagnostic radiopharmaceutical for detection and localization of acute venous thrombosis.

Dosage Form:	Sterile Solution
Strengths:	100 µg P280/20 mCi ^{99m} Tc/1-3 mL Saline
Route of Administration:	Intravenous
Dispensed:	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

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).

Molecular Formula: C₁₁₂H₁₆₂N₃₆O₄₃S₁₀; Molecular Weight: 3021.4



RELATED DOCUMENTS: None

CONSULTS: None.

REMARKS/COMMENTS:

Application is deficient on many issues, from clarification requirements on certain sections of submission, to release specifications on the P280 bulk peptide, drug product and drug substance and methods validation. Most of these deficiencies could be resolved by commitments. Studies on impurity profile and stability are detailed and the submission is generally of adequate quality.

Requests for inspection were filed by EER on 9/11/97 and another for a trademark review was filed to the nomenclature committee on 9/25/97. Results of these requests are still pending but these will be concluded before a final action on the NDA is determined.

CONCLUSION & RECOMMENDATIONS:

A list of deficiencies is attached . NDA 20,887 is considered approvable pending resolution of the CMC deficiencies, trademark issues and satisfactory cGMP inspection.

IS! *12/4/97*
Dany Salako, Ph.D.
Review Chemist

APPEARS THIS WAY
ON ORIGINAL

- CC:Orig. NDA #20,887
- HFD-160/Division File
- HFD-160/Medical Officer/Zolman
- HFD-160/Chemist/Salako
- HFD-160/Toxicologist/Laniyonu
- HFD-160/Pharmacokineticist/Udoh
- HFD-160/CSO/Ferre-Hockensmith
- HFD-160/Chemistry Team Leader/Leutzinger
- HFD-820/DNDCII/Gibbs

12/9/97
IS!

APPEARS THIS WAY
ON ORIGINAL

ADDENDUM

TO: Reviews # 1 (dated, 12-04-97), NDA 20-887
FOR: Kit for the Preparation of Technetium Tc 99m Apctide
(ACUTEK); Diatide, Inc

FROM: Eldon E. Leutzinger, Ph.D., DNDCII /S/
CHEMISTRY TEAM LEADER, DNDCII
Division of Medical Imaging and Radiopharmaceutical
Drug Products (HFD-160)

DATE: 8/28/98

RE: Categorical Exclusion

APPEARS THIS WAY
ON ORIGINAL

The applicant (Diatide, Inc.) submitted an Environment Assessment (EA) report, found in vol. 1.7, pages 195-201. Along with data on chemical reagents used, waste, disposal sites and procedures, etc., there was an account of controls and calculations

(aquatic). These calculations are on pages 199-200 in the above indicated report

.....
This estimated concentration of the active moiety at the point of entry into the aquatic environment is consistent with the current regulations, 21 CFR 25.31(b). On 10/27/97, Diatide, Inc. filed a claim for the categorical exclusion. The chemistry reviewer arrived at the conclusion in Chemistry Review #1 that Diatide's request for the categorical exclusion was acceptable on the basis of the calculated EIS. I concurred with this conclusion based on their calculations and the criteria required to be met for categorical exclusion in the case of an NDA, date of sign-off on the chemistry review.

APPEARS THIS WAY
ON ORIGINAL

cc: Orig. NDA 20-887
HFD-160/Division File
HFD-160/Project Manager/Ferre-Hockensmith
HFD-160/Chemist/Harapanhalli