CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Memorandum
Clinical Pharmacology and Biopharmaceutics Review

NDA: **21-012**

Title: NeoTect

Reviewer: Alfredo R. Sancho, Ph.D. Serial No.: N000 BZ
Submission Date: 17 June 1999 Review Date: 15 July 1999

Type of Submission: Applicant Amendment of response to Information Request of December 16, 1998.

Dosage: Intravenous administration of 50-μg peptide from a lyophilized vial.
Indication: Scintigraphic imaging of malignant tumors in the lung.

Sponsor: Diatide, Inc.
Address: 9 Delta Drive, Londonderry, NH 03053

SYNOPSIS

The original NDA 21-012 application (NeoTect: Kit for the Preparation of Technetium Tc 99m Depreotide Injection) was submitted on June 15, 1998. An approvable letter dated December 12, 1998 was issued for this product "as a scintigraphic imaging agent indicated to identify somastostatin receptor bearing pulmonary masses in patients who are highly suspect for malignancy and have pulmonary lesions on computed tomography". Prior to approval, the Applicant was requested to submit dosimetry data for Study 829-10 to this NDA application.

The applicant provided the dosimetry information requested (Study 829-10) on January 21, 1999. After review of this data and comparison with the dosimetry from Study 829-12, a fax was sent to the applicant on June 11, 1999 stating: "*Please provide an explanation for discrepencies in dosimetry data submitted in study report 829-10 and study report 829-12. Why was the dosimetry from study report 829-10 not included in the original NDA submission?*" To this, the applicant responded on June 17, 1999.

This review is focused solely on the last communication -and the data included- from the applicant dated June 17, 1999. For other issues, please refer to prior NDA 21-012 reviews of communications and data.

RESULTS

For study 829-10, the applicant states that, the methods used to determine the region-of-interest (ROI) data were not clear and were not readily reproducible. Thus, integration of the this data with that of study 829-12 was not feasible.

An analysis of the pharmacokinetic profiles from the two studies, performed by the applicant, demonstrated consistency between reported parameter estimates. The applicant provided Blood clearance data profiles. The data from study 829-10 were calculated on a per-gram of whole blood, while for study 829-12 the data were calculated on a per-gram of plasma. For comparative purposes the 829-12 data were corrected using an estimated 42% hematocrit. Data from study 829-12 were analyzed using

On the basis of the applicant's own discussion points mentioned above, i.e., [redacted] data were not clear nor readily reproducible, the applicant elected to include only the dosimetry data from study 829-12 in the NDA application.

COMMENTS

Although there are technical and logistical reasons for the applicant to exclude the dosimetry data from study 829-10 from the NDA application, the scientific merits of such data should not be underestimated. Moreover, it is common practice by applicants to submit all relevant data obtained in any study during a drug product development. If the data has limitations, the applicant should state so and explain why. For the purpose of this NDA application, study 829-10 and the data resulting from it, is to be considered supportive in nature, not pivotal to the resolution of this review.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the NDA 20-012 information and data submitted June 17, 1999. The information and data that was provided in this particular communication from the applicant properly addresses the issue in question. The Comments section of this document should be sent to the sponsor. Furthermore, there are pending issues that still need to be addressed by the applicant, which stemmed from the applicant's own communication dated 21 January 1999.

/S/ 22 July '99

APPEARS THIS WAY
ON ORIGINAL

Alfredo R. Sancho, Ph.D.
Clinical Pharmacologist/Pharmacokinetic Reviewer
Radiopharmaceuticals and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/ 7/22/99

APPEARS THIS WAY
ON ORIGINAL

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

Cc: HFD-160 NDA 21-012 (1x); DIV.FILE (1x); MOORE (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG, LESKO
CDR Attn.: Barbara Murphy

Clinical Pharmacology and Biopharmaceutics Review

NDA: **21-012**

Title: NeoTect

Reviewer: Alfredo R. Sancho, Ph.D.
Submission Date: 21 January 1999

Serial No.: BZ
Review Date: 04 June 1999

Type of Submission: Applicant response to Information Request of December 16, 1998.

Dosage: Intravenous administration of 50-μg peptide from a lyophilized vial.
Indication: Scintigraphic imaging of malignant tumors in the lung.

Sponsor: Diatide, Inc.
Address: 9 Delta Drive, Londonderry, NH 03053

SYNOPSIS

The original NDA 21-012 application (NeoTect: Kit for the Preparation of Technetium Tc 99m Depreotide Injection) was submitted on June 15, 1998. This application was approvable "as a scintigraphic imaging agent indicated to identify somastostatin receptor bearing pulmonary masses in patients who are highly suspect for malignancy and have pulmonary lesions on computed tomography".

Prior to approval, the Applicant was requested to address several issues. The present document reviews the response to the following Human Biopharmaceutics issue:

> "The application did not provide dosimetry information obtained from Study 829-10 in the current NDA. This information was submitted in the IND (Submission date 10/31/95). Please submit this information to the NDA."

RESULTS FROM STUDY 829-10

A total of 15 subjects from two different studies and sites (Harbor n=10, and NYC n=5) were included in the dosimetry data provided by the applicant. A total of 5 time points were assessed for all organs: 10 minutes, 1, 2, and 4 hours, followed by the fifth time point that varied between 20.4 and 24.9 hours post injection. The amount of basic information obtained from these subjects was sufficient to properly estimate the absorbed dose to critical organ-tissues and whole body. The [redacted] and the male adult phantom [redacted] were used to estimate the absorbed doses for each subject independently.

Overall there were six organs that had estimated mean (n=15) absorbed doses higher than 0.040 rad/mCi. These were: kidneys 0.24 rad/mCi, spleen 0.15 rad/mCi, thyroid 0.054 rad/mCi, bone marrow 0.049 rad/mCi, liver 0.048 rad/mCi, and bone surface 0.041 rad/mCi.

The estimated lung residence time -the intended target tissue- between all subjects showed a high level of variability. Some of these subjects may have estimated high values for lung residence time due to that they had three time points, instead of the proposed five time points.

Some subjects included in this dosimetry data base did not have all their organ residence times calculated, *e.g.* 9/15 subjects from both groups did not have thyroid residence times calculated.

Marked retention was observed in the kidneys, liver, and spleen at the final time point (20.4 to 24.9 hours post administration). This large mean dose estimate reflects long-term retention of the drug product in these organs.

SAFETY

Although in the dosimetry data provided by the Applicant it can be observed that there are six organ-tissues that have an estimated absorbed higher than 0.040 rad/mCi, this is mainly due to self-dose and not from neighboring organs. Within these six identified organs, the spleen and bone marrow are included. This may be of safety concerns for the hematopoietic marrow due to extended or repeated ionizing radiation exposure.

There is a known affinity of 99mTc-species for Thyroid tissue, which may affected by exogenous iodine, thyroid hormones, and thyroid-stimulating hormone. The radiation exposure to patients receiving the proposed drug product may be an issue, particularly if the product is administered repeatedly within a year.

COMMENTS TO THE APPLICANT

Based on the dosimetry results submitted under the original NDA (Pivotal Study 829-12) and in the current submission (Supportive Study 829-10), the following comments should be forwarded to the sponsor:

1. For the Harbor study No. 829-10, the provided dosimetry data several of the subjects did not have absorbed dose and/or residence time for all the tissues, e.g., 9 of 10 subjects from the Harbor study did not have Thyroid absorbed dose estimates. Please, using the data base at hand, recalculate the absorbed dose estimates from all 15 subjects for all organs, particularly the six organs that demonstrated "high" absorbed doses, kidneys, liver, bone marrow, bone surface, spleen, and thyroid.
2. There is no in-vivo stability data for this compound in human blood at different time points after administration. If available, please provide in-vivo stability data in human blood up to 24 hours post-administration of the proposed drug product. Please characterize these results by percentage of radiolabel alone, radiolabel-ligand, and ligand alone.
3. There is no information on what portion of the proposed drug product is eliminated through the liver or the kidneys. The dosimetry data provided demonstrate high levels of activity in the liver, kidneys, spleen and bladder, but there is no characterization of the source, e.g. radiolabel alone, and/or radiolabel-ligand. Please provide information on the nature of the excreted material that is eliminated through the kidneys and liver.
4. The observed affinity ("Thyroid trapping") of 99mTc-species found in the final form -heating step included- of this product is derived from the "*Tc99m void activity*" and "*Tc99m Lypophilic species*", which were up to 2 and 5 percent, respectively. The heating step included in the final protocol and label insert reduced these Thyroid affinity values for these identified 99mTc-species by as much as 5 percent. This was assessed by [redacted] assay of the pivotal batches of 99mTc-Depreotide kits, Lot No. 9509B01, 9609B01, and 9609B02. Due to the demonstrated affinity of these 99mTc-species for Thyroid tissue, the Applicant may find it desirable to suggest protection of the thyroid with a "Thyroid block" agent before administering this product, particularly for those patients that have some Thyroid metabolism disease or will be given this product repeatedly over a given period of time.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the NDA 21-012 (Serial No. BZ) information and data submitted January 21, 1999. The issues mentioned in the "COMMENTS TO THE APPLICANT" section need to be forwarded to the Applicant. At this time, it is recommended that this NDA submission be considered "approvable" pending the response from the Applicant, including the data requested are sufficient and appropriate to address the Agency's safety concerns.

/S/ 7/22/99

Alfredo R. Sancho, Ph.D.
Clinical Pharmacologist/Pharmacokinetic Reviewer
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/ 7/22/99

David Lee, Ph.D.
Team Leader, Pharmacokineticist
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
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Cc: HFD-160 NDA 21-012 (1x); DIV.FILE (1x); MOORE (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG, LESKO
CDR Attn.: Barbara Murphy

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Type of Submission:	Original NDA (NME)
NDA Number:	NDA 21-012
Code:	1 P
Drug:	NeoTech ™ (Kit for the preparation of Technetium Tc 99m depreotide injection)
Sponsor:	Diatide Inc.
Submission Date:	6/16/98
Reviewer:	Young Moon Choi, Ph.D.

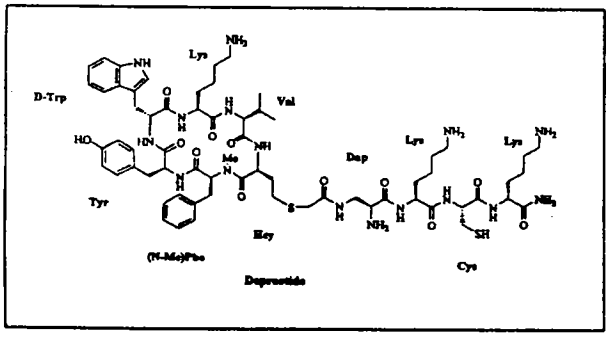
1. SYNOPSIS

NDA 21-012 for the " Kit for the preparation of Technetium Tc 99m depreotide injection", was submitted by Diatide Inc. on 6/16/98. This product was developed under IND [redacted]

The drug substance, 99m Tc depreotide, is a peptide based receptor imaging agent which offers potential utility in the scintigraphic imaging of malignant tumors in the lung. Intravenous bolus administration is recommended.

Currently available imaging techniques, such as chest X-ray and computed tomography, are not capable of distinguishing malignant from non-malignant tissue. Therefore, the advantage of specific indication may warrant the priority review status.

Depreotide is a synthetic ten amino acid peptide, which comprises of two domains: (1) a cyclic hexapeptide domain, which contains the somatostatin type receptor-binding sequence, -Tyr-D-Trp-Lys-Val-, and (2) a tetrapeptide domain, -β-diaminopropionyl-Lys-Cys-, which forms a chelate complex with 99m Tc .



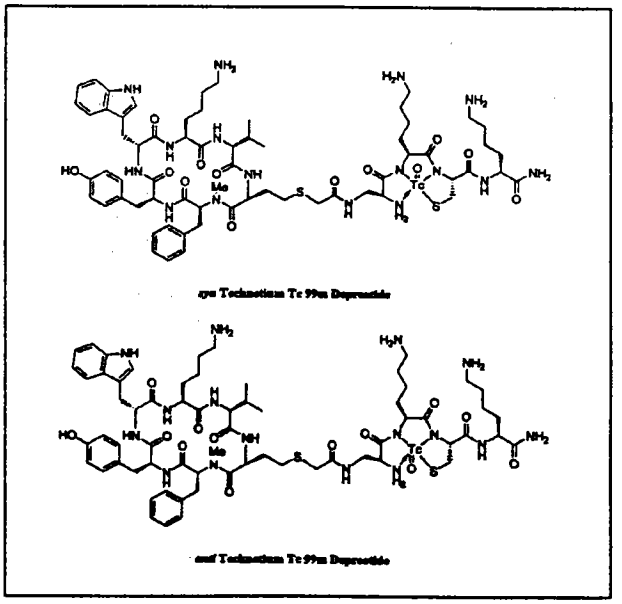


Figure 1. Chemical structure of depreotide and Technetium Tc99m depreotide

There are two isomers, syn and anti, of Technetium Tc 99m P829 present in the reconstituted Kit for the Preparation of Technetium Tc 99m P829. The anti isomer is predominant with an approximate ratio of syn/anti = 0.1. Anti isomer has a higher affinity than syn isomer. The formation ratio of syn and anti appeared to be consistent from batch to batch.

NDA 21-012 submission contained two pharmacokinetic studies (Protocol 829-10 and 12) and a pharmacodynamic study (Protocol 829-13). In addition, as per the agency's request, the sponsor submitted the two in vitro studies: (1) Evaluation of the compatibility of 99m Tc depreotide injection prepared with decayed generator elute with human blood or serum (Protocol No. R4.23) and (2) Distribution of 99m Tc depreotide between human blood components in vitro (Protocol No. R.4.38).

The study design is summarized in Table I.

Pharmacokinetic studies used to-be-marketed formulation, except one is heat treated during the final drug preparation.

Table I. Human pharmacokinetic studies of Kit for the preparation of Technetium 99m Tc depreotide injection.

Study No.	Design N=No. of subjects recruited (male/female)	Dose	Remarks
829-10	Phase I, Nonrandomized, open label, single dose safety, tolerance; Pharmacokinetics; normal volunteers; n=17 (9/8)	50 µg P829 peptide (depreotide), 10 mCi 99m Tc	[redacted] 12 out of 17 subjects were reported for PK.
829-12	Phase I, single center, open label; pharmacokinetics and radiation dosimetry; normal and patients; n=23 (14/9); 12 normal (6/6/); 5 hepatic dysfunction (4/1); 4 renal dysfunction (2/2); 2 lung cancer (2/0)	50 µg P829 peptide (depreotide), 15-20 mCi 99m Tc	[redacted] 17 out of 23 were reported for PK: normal (4/5), hepatic patients (2/1), renal patients (2/1), lung cancer (2/0)
829-13	Phase I, single center, open label study; pharmacodynamics and immunogenicity in normal volunteers; n=9 (5/4)	50 µg P829 peptide (depreotide), No radioactivity	The oral glucose tolerance test. All the 9 subjects were reported.
R4.23	In vitro evaluation of the compatibility of 99m Tc depreotide injection prepared with decayed generator elute with human blood or serum.	99m Tc depreotide; 1:4 or 1:8 dilution	Human blood and serum obtained from 1 male and 1 female.
R4.38	Distribution of 99m Tc depreotide between human components in vitro.	10nM final whole blood concentration.	Citrated human whole blood.

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has completed the review on the submission to NDA 21-012 and has found the information inadequate from a clinical pharmacology and biopharmaceutic perspective.

The deficiencies in the clinical pharmacology and biopharmaceutics section may be summarized as follows:

(1) Lack of appropriate information on the elimination of Technetium Tc 99m depreotide.

Due to (1) the failure of the collecting samples (Protocol violation), (2) limited number of subjects, (3) variation of the data from study to study, and (4) insufficient information on metabolite, the elimination of the Technetium 99m Tc depreotide has not been appropriately elucidated.

The renal clearance of 99m Tc depreotide appeared to be only 10-15 % of the total clearance. Due to a protocol violation, the fecal samples were not collected. Therefore, the application lacks information on the remaining 90 % of the administered product.

There is no supportive data for the other major route(s) of elimination. The animal data may not be supportive for the elucidation of the major elimination route since the majority of the radioactivity appeared to be eliminated through renal route in animals. Furthermore, in assessing dosimetry, it has been stated that "the total clearance is mainly through renal route, and radioactivity through bile elimination is negligible." However, there is no quantitative data regarding the bile secretion of the radioactivity.

Elimination information needs to be collected in additional subjects, due to the variability of pharmacokinetic parameters obtained in studies 829-10 and 829-12 (Please refer to Table II on page 3). Study 829-12, in which the formulation was tested as recommended in the proposed package insert, has been considered to be appropriate to evaluate.

Table II. Comparison of the pharmacokinetic parameters of study 829-10 and 829-12

Study Number	Study 829-10	Study 829-12
Normal Subjects (male/female)	12 (6/6)	9 (4/5)
Vss (L/kg) **	3.04 ± 0.87	1.56 ± 0.85
CL total (ml/min/kg) **	3.87 ± 0.93	2.12 ± 1.30

** represents $P<0.05$.

The clearance values appear to be different by gender including patients (Please refer to the individual study summary in Appendix 1-2 in this review). This reviewer's gender analysis indicates that (1) in study 829-10, there was a gender effect, however, (2) in study 829-12 gender effect appears not to be statistically different due to the limited number of subjects and variation of the data. The evaluated number of normal subjects was 4 males and 5 females (Table III).

Table III. Comparison of the pharmacokinetic parameters of male and female

Study Number	Parameters	Normal male	Normal female
Study 829-12	Vss (L/kg)	1.41 ± 0.66 (n=4)	1.68 ± 1.04 (n=5)
	CL total (ml/min/kg) [a]	2.68 ± 1.73 (n=4)	1.68 ± 0.75 (n=5)
Study 829-10	Vss (L/kg)	2.67 ± 0.78 (n=6)	3.40 ± 1.04 (n=6)
	CL total (ml/min/kg) *	4.54 ± 0.96 (n=6)	3.41 ± 0.63 (n=6)

[a] P value is 0.278. However, it should be noted that the difference might not be seen due to the variation and limited number of subjects.
* represents $P< 0.05$.

No data were provided regarding metabolites despite the evidence of the metabolism in the blood and urine samples (Please refer to the Table IV on page 4). The [redacted] analysis of the blood and urine samples indicates that the 20 to 40 % of the radioactivity in blood and urine appeared to be not associated with parent compound.

Table IV. The percent of radioactivity associated with the parent peptide in blood and urine.

Blood (n=21-22)		Urine (n=20-21)	
15 min	84 ± 23 %	0-1 hr urine	64 ± 19 %
30 min	82 ± 18 %		
1 hour	84 ± 19 %	1-4 hr urine	61 ± 16 %
2 hour	71 ± 20 %		

Based on the above findings, the additional pharmacokinetics studies need to be conducted to appropriately elucidate the elimination of the drug substance.

(2) Lack of information on the pharmacokinetics of depreotide (peptide moiety)

It should be noted that the pharmacokinetic analyses in both studies , 829-10 and –12, are not for depreotide, but for the radioactivity. Due to the failure of developing the analytical method for depreotide, the applicant could not provide the depreotide disposition data in human.

Furthermore, no study has been conducted over the recommended dose of 50μg of depreotide. Since the depreotide has high affinity to somatostatin receptor, the somatostatin-like pharmacological/toxic effect is expected after administration of depreotide into human. Although the sponsor provided safety data and glucose tolerance test results, the studies have been done only up to the recommended dose, 50μg of depreotide.

Since there is a potential for differences in pharmacokinetics and tissue distribution of depreotide in the disease state (Please refer to the Table V and the tissue distribution data under the section covering dosimetry in this review), dose adjustment may be needed in the patients.

Table V. Comparison of the pharmacokinetic parameters in normal subjects and patients.

Study No.	Subjects	Vss (L/kg)	CL total (ml/min/kg)	CLrenal (ml/min/kg)
829-10	Normal	3.04 (n=12)	3.87 (n=12)	0.26 (n=12)
829-12	Normal	1.56 (n=9)	2.12 (n=9)	0.37 (n=4)
	Hepatic dysfunction	1.7 (n=3)	2.45 (n=3)	0.24 (n=1)
	Renal Dysfunction	1.49 (n=3)	1.49 (n=3)	None evaluated
	Lung cancer	0.94 (n=2)	1.64 (n=2)	None evaluated

(3) Lack of appropriate information regarding the pharmacokinetics in diseased population.
Any statistical analysis is not possible due to the limited number of subjects with lung cancer (n=2), or hepatic (n=3) or renal (n=3) patients.
However, the applicant reported that the patients have different tissue distribution from normal subjects and there is a potential difference in pharmacokinetics (Please refer to the Table V and tissue distribution data under the dosimetry section in this review).

(4) Lack of sufficient information regarding special populations
Studies have not been conducted to assess the disposition of 99m Tc depreotide in geriatrics, pediatrics, and nursing mother.

The applicant reported a correlation of age vs. pharmacokinetic parameters in the study report of 829-10. However, whether age can affect the pharmacokinetics of depreotide or not is inconclusive due to the following reason:
As stated above, the studies 829-10 and 829-12 appear different (Please refer to the Table II on page 3). Therefore, Study 829-12, in which the formulation was tested as recommended in the proposed package insert, could be used. However, the range of age was between 19-28 years old in study 829-12. Therefore, it appears inappropriate to test age affect on the pharmacokinetics of Technetium Tc 99m depreotide within this age range.

2. RECOMMENDATION **Approvable**

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-012. Based on the information presented in the NDA, this application is *approvable*, provided the Labeling Comments and the Comments to the Applicant that need to be adequately addressed by the applicant.

The items and studies in the Comments to the Applicant can be addressed post-approval provided that the information that is to be obtained from the recommended studies is not determined to be needed prior to approval from a safety and efficacy perspective.

The applicant should submit pharmacokinetic study protocols to the agency for review prior to initiating the study.

APPEARS THIS WAY
ON ORIGINAL

/S/ 11/27/98

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

/S/ 11/25/98

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

Required Office Level Biopharm Briefing Day: 10/13/98

CC:		
	HFD-160	NDA 21-012/ DIV FILE/CSO
	HFD-870	JHUNT/ DLEE/ MECHEN/YMCHOI
	HFD-880	JLAZOR/ASELEN
	HFD-860	MMETHA
	HFD-850	LLESKO/SMHUANG

APPEARS THIS WAY
ON ORIGINAL

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- Appendix -2. Applicant Labeling

3. BACKGROUND INFORMATION

NDA 21-012 for the " Kit for the preparation of Technetium Tc 99m depreotide injection", was submitted by Diatide Inc. on 6/16/98. This product was developed under IND 47, 020.

The drug substance, Technetium Tc 99m depreotide, is a peptide based receptor imaging agent which offers potential utility in the scintigraphic imaging of malignant tumors in the lung by intravenous bolus injection. Currently available imaging techniques, such as chest X-ray and computed tomography, are not capable of distinguishing malignant from non-malignant tissue. Therefore, the advantage of specific indication may warrant the priority review status.

Depreotide is a synthetic peptide of ten amino acids, which comprises two domains: (1) a cyclic hexapeptide domain, which contains the somatostatin type receptor-binding sequence, -Tyr-D-Trp-Lys-Val-, and (2) a tetrapeptide domain, -β-diaminopropionyl-Lys-Cys-, which forms a chelate complex with 99m Tc (Please refer to the Figure 1 on page 1.)

Somatostatin is a peptide having the amino acid sequence Ala-Gly-Cys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cyc (underline indicates Cyc-to-Cys disulfide bridge). It is produced by the hypothalamus and pancreas and, through binding to specific receptors, inhibits the secretion of many hormones and growth factors. To date, five sub-types of high-affinity somatostatin type receptors (SSTRs) have been identified. Although SSTRs are expressed on normal tissues, they are expressed to a greater extent (hyper-expressed) by many malignant tumors. This hyperexpression of SSTRs by malignant tumors provides the basis for a means of differentiating malignant tissues from normal tissues by nuclear imaging using an SSTR-binding radiotracer.

3-1. Chemistry

Commercial Name:	NeoTech ™
Drug Product Name:	Kit for the preparation of Technetium Tc 99m Depreotide
Code Name:	P829
Therapeutic class:	Diagnostic
Chemical Name:	Cyclo(-L-homocysteinyl-N-methyl-L-phenyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl),(1→1')-sulfide with 3-[(mercaptoacetyl)amino]-L-alanyl-L-lysyl-L-cycteinyl-L-lysine amide, trifluoroacetate salt
Molecular Formula:	$C_{65}H_{96}N_{16}O_{12}S_2$ (net)
Molecular Weight:	1357.7

Chemical Structure:
There are two isomers of Technetium Tc 99m P829 present in the reconstituted Kit for the Preparation of Technetium Tc 99m P829, designated syn and anti (Please refer to the Figure 1 on page 1.) The anti is predominant with an approximate ratio of syn/anti = 0.1. Anti has a higher affinity than syn. Average IC 50 values for the syn isomer was 0.89 ± 0.15 nM compared to 0.15 ± 0.04 nM for the anti isomer in the in vitro binding study on AR42J tumor membrane.) The

3-2. Mechanism of diagnostic action

The applicant stated in the package insert that :
"The mechanism of its diagnostic action in human is not known at the present time; however, in vitro data and studies in laboratory animals suggest that the radiopharmaceutical binds to and localizes with somatostatin receptors expressed in tumor-bearing and normal tissues. "

3-3. Formulation

Table VI. Formulation.

Component	Remarks
50 µg P829 peptide trifluoroacetate (Depreotide)	available as individual vials or as packs of five
50 µg stannous chloride	
5 mg sodium glucoheptonate dihydrate	
100 µg disodium edetate dihydrate	
NaOH or HCl for adjustment of pH 7.4 ± 0.1	

3-4. Indications and usage

The applicant stated in the package insert that :
"Technitium Tc 99m depreotide is indicated for scintigraphic imaging of malignant tumors in the lung."

3-5. Dosage administration

The applicant stated in the package insert that :
"For imaging, Technitium Tc 99m depreotide is administered in a single dose of approximately 50 μg peptide labeled with 15 to 20 mCi technitium-99m. Imaging may begin one hour following administration of the agent.
Only one patient dose should be drawn from each reconstituted vial.
Dose adjustment has not been established in patients with renal insufficiency, or in pediatric or geriatric patients."

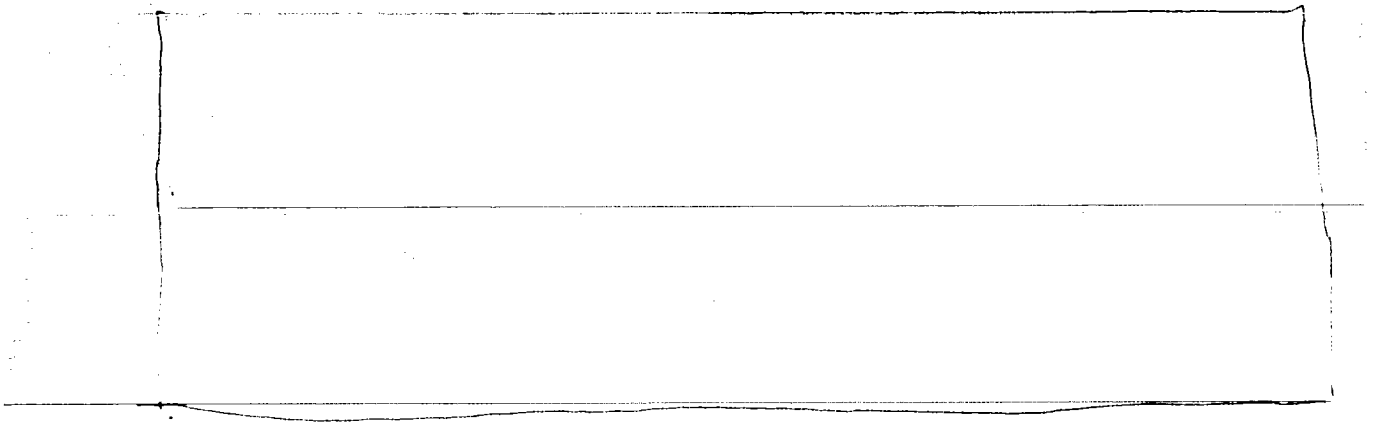
4. PHARMACOKINETICS

Each pharmacokinetic study was reviewed and summarized in Appendix. This section mainly contains the reviewer's comments on the issues from clinical pharmacology and biopharmaceutic perspectives.

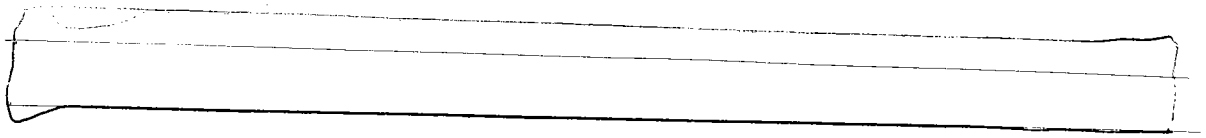
4-1. Dose selection

As indicated in Table I, no dose ranging study was conducted for pharmacokinetics. The one dose of 50 μg of depreotide and 10-20 mCi of Tc 99m was used for pharmacokinetic studies.

Based on the communication with the reviewing medical officer, Dr. Sally Loewke, it appears that the recommended dose has been selected by the pharmacodynamic study (829-23; this study has not been provided in item 6) on three different doses , i.e., 10, 20, and 50 μg of depreotide and 5, 10, and 20 mCi of Tc 99m. However, the pharmacodynamic end point, i.e., the tumor vs. background imaging brightness ratio, appeared to be similar in all nine combinations. The applicant chose the highest dose. However, no quantitative interpretation has been provided.



4-3. Pharmacokinetics of depreotide



This reviewer is of the opinion that the pharmacokinetic study of depreotide should be performed based on the following concerns:

Since the depreotide has high affinity to somatostatin receptor, the somatostatin-like pharmacological/toxic effects are expected after administration of depreotide into human. Although the sponsor provided safety data and glucose tolerance test results, the studies have been conducted only up to the recommended dose, 50μg of depreotide. No safety and efficacy study has been done over the recommended dose of 50μg of depreotide (Based on the communication with reviewing medical officer, Dr. Sally Loewke).

There are potential differences in the pharmacokinetics and tissue distribution of the depreotide in disease status (Please refer to the Table IV and tissue distribution data under the section of dosimetry review on page 17 in this review). The dose adjustment may be needed in patients groups.

Animal data may not be extrapolated to the human due to the different pharmacokinetics and elimination pattern: Rat has approximately 6 times greater clearance than human . Furthermore, the major elimination route appeared to be renal route. (Based on the communication with the Pharm/Tox reviewer, Dr. David Bailey)

4-4. Radioactivity pharmacokinetics after the administration of Technetium Tc 99m depreotide.

From the results of two pharmacokinetic studies, the applicant stated in the package insert that : "Studies in normal volunteers and in patients have demonstrated that the tracer confers three-compartment pharmacokinetics with a distribution half-life of less than five minutes and a terminal half-life of about 20 hours, and a steady state volume of distribution of 1.5 to 3 liters/kg. Total clearance averaged 1.5 to 4 ml/min/kg. Renal clearance averaged about 0.2 to 0.4 ml/min/kg. External whole-body gamma scintigraphy showed highest localization of radioactivity in the abdomen. Six to 17 % of the injected dose of radioactivity appeared in urine at four hours after injection. No clinically important differences in the disposition of radioactivity appeared between men and women."

However, this reviewer is of the opinion that the radioactive pharmacokinetics is not sufficient and the applicant's statement in the package insert should be corrected. This reviewer's opinion is based on the following findings:

(1) In the applicant's statement, pharmacokinetic data were combined for normal subjects and patients of both gender. However, the data should not be combined because:

The volume of distribution and clearance appeared to be statistically significantly different from study to study (Please refer to the reviewer's statistical analysis and comparison of the pharmacokinetic parameters in Table II on page 3). The reason(s) of the significant difference of pharmacokinetic values from study 829-10 and 829-12 should be elucidated.

There appeared to be a gender effect on the clearance. (Please refer to the applicants report of the study 829-12 in Appendix 1-2.)

There are potential differences in pharmacokinetics and in tissue distribution in renally and hepatically impaired subjects and lung cancer patients (Please refer to the Table V on page 4 and tissue distribution data in dosimetry report). It should be noted that the statistical analysis is not conclusive due to the limited number of subjects.

(2) In data analyses, the applicant states that subjects were excluded because the subject's data is variable from the others or unable to fit to triexponential model. It may not be an appropriate reason to exclude these subjects so called "outliers". (Please refer to the Table I on page 2 and individual study summary in Appendix 1-1 and 1-2).

(3) The elimination of the radioactivity has not been appropriately described. It should be noted that there were protocol violations: The fecal samples were not collected, which may be critical for accurate evaluation of the elimination, because:

The renal clearance of the 99m Tc depreotide appeared only 10-15 % of the total clearance and the application lacks an adequate information on the rest of 90 % of the elimination.

Based on the communication with the Pharm/Tox reviewer, Dr. David Bailey, the animal data may not be supportive for the elucidation of the major elimination route since the majority of the radioactivity appeared to be eliminated through renal route in animals.

Furthermore, in dosimetry analysis, it has been stated that "the total clearance is mainly through renal route, and radioactivity through bile elimination is negligible." However, there is no quantitative data supporting the bile secretion of the radioactivity.

4-5. Metabolism

The radioactive metabolites in the blood or urine of subjects receiving 99m Tc depreotide were assessed by a [redacted] method with fraction collection (Study 829-12).

The quantitative analysis by this reviewer shows that the significant portion of the radioactivity (20-40 %) appeared to be not associated with the depreotide (Please refer to the Table IV on page 4).

Based on the communication with the reviewing chemist, Dr. Ravi Harapanhalli, the allowable radioactivity purity was 80 %. Therefore, approximately 20 % may be expected as impurity. However, more than 20 % should be considered as metabolite. In Figure 2 on page 13, metabolites appeared earlier than depreotide in urine.

No interpretations were provided regarding the significance of the radioactive metabolites. Yet, the sponsor concluded and stated under the metabolism section in the proposed package insert that the "Plasma radioactivity is predominantly (> 90%) in parent form. The majority of the radioactivity excreted in urine is in parent form."
The renal clearance is only 10-15 % of the total clearance. The applicant reported that the bile secretion appeared to be negligible. However, no quantitative data were provided.

In this context, this reviewer is of the opinion that the applicant should elucidate the metabolism of the drug product.

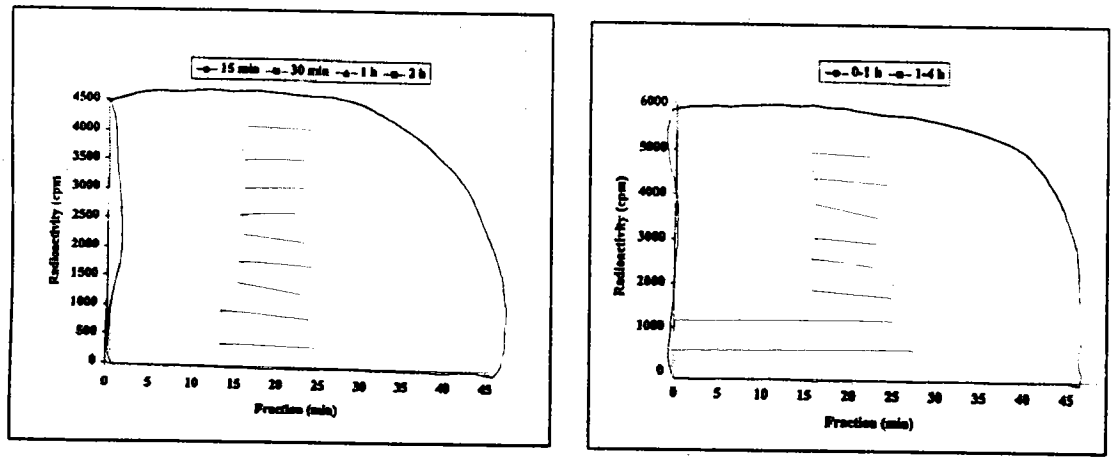


Figure 2 data of blood (left panel) and urine (right panel). Fractions #17-23 were considered as a depreotide.

4-6. Protein binding information

In vivo plasma protein binding of total radioactivity was determined by the method using the 5-min plasma sample (Study 829-12). The overall (including patients) mean ± SD plasma protein binding was 12.1 ± 2.8 %.
Since the applicant provided overall data without discriminating gender and disease status, this reviewer classified the data by gender. There were no gender effect in protein binding. However, a lung cancer patient appeared to have approximately two times higher protein binding value than normal subjects (Please refer to the following Table VIII).

Table X. The comparison of the protein binding in normal subjects and patients.

Study No.	Subjects	Protein binding % bound
829-12	Normal	11.2 ± 2.97 (n=11)
	Hepatic dysfunction	11.4 ± 1.89 (n=5)
	Renal Dysfunction	11.7 ± 2.05 (n=4)
	Lung cancer	20.7 (n=1)

This reviewer is of the opinion that the protein binding may affect significantly the disposition of the Technetium Tc 99m depreotide. Such an effect can be seen in the Table V on page 4; lung cancer patients have reduced free fraction of the drug in blood, and thus reduced clearance and volume of distribution. This seems reasonable since this drug has low clearance value and can be classified as low extraction ratio drug. This reviewer is also of the opinion that the protein binding study should be conducted in the clinically relavant concentration range, i.e., at least three (high, low and in between) concentrations.

4-7. Radioactivity pharmacokinetics in special population

4-7-1. Target population: Lung cancer patients

The two lung cancer patients were studied. Any conclusion is not possible due to the limited number of samples.

However, it should be noted that the biodistribution of radioactivity in lung tissue appeared more extensive than that of normal subjects. The lung residence time was 68 % longer than normal. The radiation absorbed dose appeared to be more extensive than the other tissues (Please refer to the dosimetry analysis in this review). Also, the protein binding, volume of distribution, and clearance values appeared to be different from the normal values.
Therefore, it is recommended that the sponsor should examine the potential differences of the disposition of radioactivity in target population, and the gender difference in that population.

4-7-2. Hepatic and renal patients

Three hepatic patients (2 males and 1 female subjects) and 4 renal patients (2 males and 2 females) have been reported. It may be difficult to conclude whether the pharmacokinetics in these patient populations is identical or not with normal subjects.
It should be noted that the biodistribution data appeared to be different from normal subjects: In hepatic patients, the two tissues appeared to be different in radioactivity biodistribution, i.e., more than 30% of the normal value. In renal patients, kidney residence time decreased 45%, and liver residence time increased by 68 % . This may warrant additional study on the potential difference in disposition of the depreotide.
It is recommended that the data should be collected from more subjects to obtain a reliable conclusion.

4-7-3. Nursing Mothers

Studies have not been conducted to assess the disposition of 99m Tc depreotide in nursing mother.
In the proposed package insert, the applicant stated that :
"It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Technitium Tc 99m depreotide is administered to a nursing women. Wherever possible, infant formula should be substituted for breast milk until the Technitium has cleared from the body of the nursing woman."

4-7-5. Geriatrics and Pediatrics

Studies have not been conducted to assess the disposition of Technetium Tc 99m depreotide in geriatrics and pediatrics.

The applicant reported the correlation of age vs. pharmacokinetic parameters in the study report of 829-10. However, whether the age can affect the pharmacokinetics of the depreotide or not is inconclusive due to the following reason:
As stated above, the studies 829-10 and 829-12 appeared different (Please refer to Table II on page 3). Therefore, the study 829-12, in which the formulation was treated as recommended in the proposed package insert, could be used. However, the range of age was between 19-28 years old in the study 829-12. Therefore, it appears to be inappropriate to test the age effect on the pharmacokinetics of Technetium Tc 99m depreotide within the age range.

4-8. Drug-Drug interaction

No pharmacokinetic studies were conducted to assess possible interactions of depreotide 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 99m Tc depreotide was administered to patients receiving concomitant medication." No quantitative data from the "clinical studies" were provided to support this statement.

5. PHARMACOKINETC / PHARMACODYNAMIC (PK/PD) RELATIONS:

5-1. Imaging quality as a clinical end point

No correlation of blood concentration and imaging quality was made in the present submission.

However, this reviewer has concerns over a PK/PD relationship on the above drug based upon:
(1) radioactivity profile in blood: rapid distribution phase (less than 5 min of alpha phase half-life) and slow elimination with terminal half-life of 20 hours (Please refer to the Figure 3).
(2) characteristics of target tissue, i.e., lung which is well-perfused organ and
(3) radioactivity distribution kinetics in the tissue. The tissue data showed that the 10-min tissue distribution post dose appeared to be essentially same as 24-hour post dose distribution.

In the proposed package insert, it is recommended that the optimal imaging may be initiated after 1 hour post injection and is recommended up to 4 hours. This may be due to the fact that imaging quality can be decided not only by the intensity of radioactivity in the target organ but also by the tissue vs. blood (as a background noise source) ratio.

By considering these, it is expected that the infusion regimen may be more advantageous than bolus since infusion:
(1) will avoid the initial high blood concentration, which is a background noise source.
(2) may reach appropriate tissue/blood ratio may reach more rapidly than bolus.
(3) May require less amount of radioactivity.

Possibly, simulated PK/PD analysis may verify above infusion regimen concept. The applicant should consider exploring the usefulness and importance of PK/PD analysis.

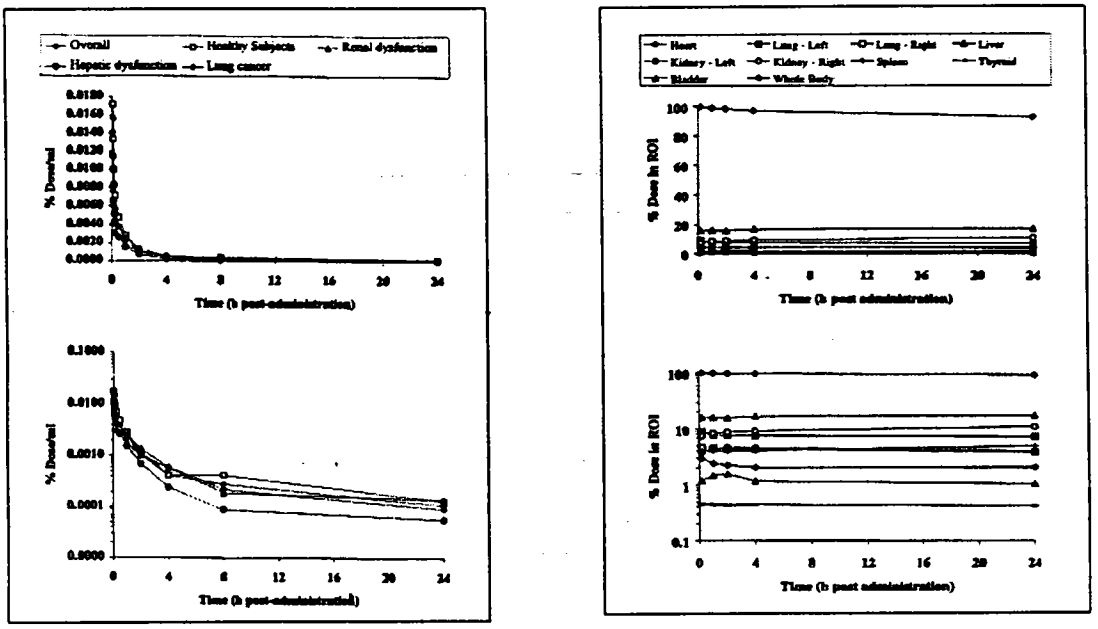


Figure 3. Blood radioactivity (left) and tissue radioactivity of the lung cancer patients (right) after intravenous bolus injection of Technetium Tc 99m depreotide.

5-2. Glucose tolerance as a clinical end point (or surrogate marker)

In study 829-13, the applicant performed a pharmacodynamic study to obtain the glucose tolerance test (GTT) and provided the report to this reviewer for the insight to the clinical pharmacology. However, the drug effect on the GTT appeared to be similar to the placebo, i.e., no effect has been observed (Please refer to the following Figure 4). Therefore, no quantitative relationship has been estabilished with the response and blood concentration level after administration of the present dose.

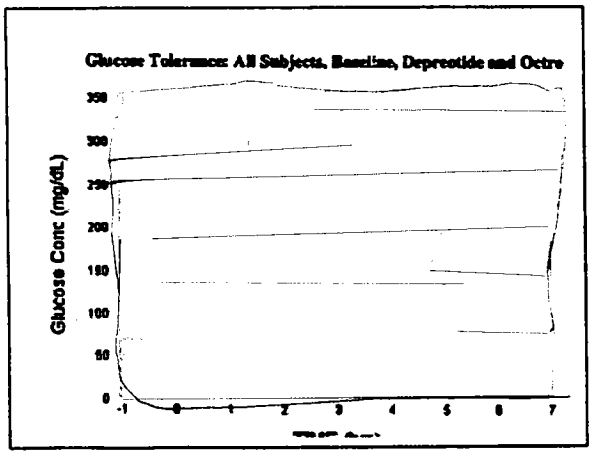
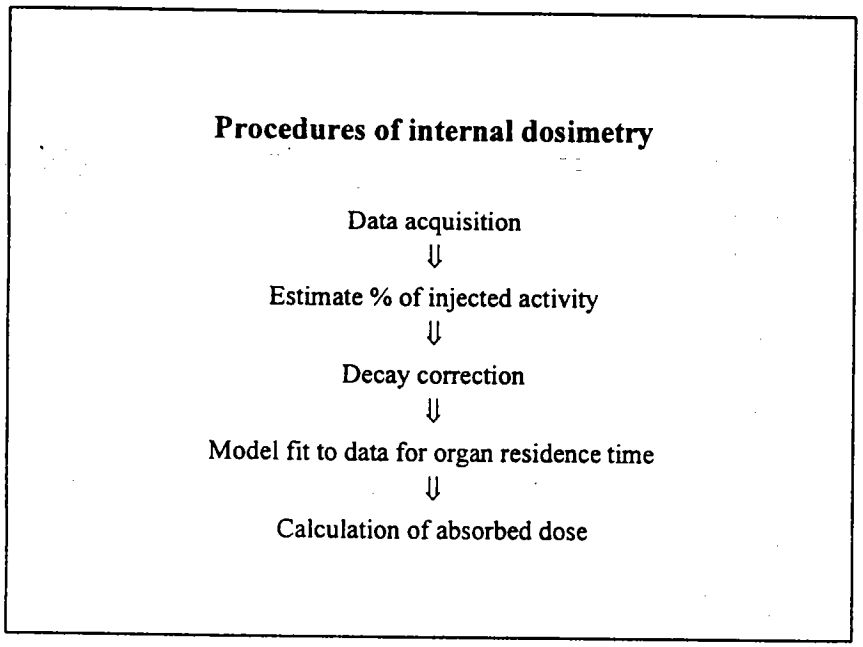


Figure 4. Glucose tolerance test result from 9 normal subjects.

6. DOSIMETRY

In using radiopharmaceutical products, either for diagnostics or therapeutic use, the radiation safety may be an equally important issue compare to pharmacological safety. Therefore, after the administration of certain amount of radioactivity, the information of the extent of biodistribution of the radioactivity in tissues as well as in whole body should be used to evaluate the radiation exposure.

The general procedures of dosimetry are as follows:



In the present submission, the applicant provided the decay corrected biodistribution data of 11 radiation source organs from 22 subjects to the [redacted]. The model fitting for organ residence time and calculation of absorbed dose were performed by the [redacted].

6-1. RADIOACTIVITY CONTENTS OF REGIONS OF INTEREST (CUMULATED RADIATION IN SOURCE ORGAN)

The time activity data describing the percent of injected activity in each source organ were mathematically treated. For each subject, multiexponential functions were fit to eleven source organ time-activity curve using a nonlinear least-square regression algorithm. These curves were numerically integrated to yield source organ residence times.

Whole body retention was estimated from the region of interest encompassing the entire body. The urinary excretion (cumulative) time-activity curve was fit to mono- or bi-exponential functions and the parameters of these curves used as input data for the dynamic bladder model. The urinary bladder was assumed to void regularly at 4.8-hour intervals.

For bone marrow, the activity in the ROI encompassing the head was assumed to be in marrow and that the activity in that marrow space was representative of all other marrow spaces. In reference man, the skull is assumed to contain 8.3 % of the total active marrow. The head ROI was also used to determine brain retention, hence the activity in this ROI was counted twice in the analysis.

The remainder of body residence time was calculated as the total residence time minus the sum of all the other listed organ residence time. Due to the assumption in marrow, there were cases that the remainder of the body value appeared to be minus. In those cases, the value was assumed zero. The consequence of this appeared to be 5-10 % of underestimation of remainder of the body average value.

The results are presented in the Table IX.

Table IX. Average organ residence time. Data obtained from the study report of 829-12.

Average Organ Residence Times for Tc-99m P829
(Healthy and Diseased Subjects)

ORGAN	Healthy Subjects (n=11) hours	Diseased Subjects (n=11) hours	Liver Disease (n=5) hours	Renal Disease (n=4) hours	Lung Cancer (n=2) hours
Brain	0.14	0.12	0.13	0.14	0.07
Breast	0.25	0.36	0.28	0.40	NA
Heart	0.16	0.23	0.23	0.26	0.19
Kidney	1.95	1.39	1.71	1.07	1.25
Liver	1.07	1.62	1.55	1.80	1.45
Lungs	0.62	0.82	0.70	0.86	1.04
Marrow	3.00	2.64	2.70	2.85	2.08
Spleen	0.41	0.38	0.43	0.32	0.37
Testes	0.08	0.10	0.10	0.11	0.08
Thyroid	0.03	0.04	0.03	0.05	0.04
Uterus	0.11	0.06	0.06	NA	NA
Remainder	0.70	0.81	0.50	0.72	1.76
Urinary Bladder	0.18	0.11	0.17	0.06	0.08
Whole Body	8.08	8.19	8.04	8.32	8.32

NA = Not Applicable or not assessed

6-2. ABSORBED DOSE (RADIATION ENERGY) ESTIMATION

The MIRDOSE 3.1 software was used to estimate the absorbed doses for each subject separately. Male and female subjects' dose estimates were calculated using Adult Male and Female phantoms, respectively.

The results are presented in the following Table X.

Table X. Absorbed dose. Data obtained from the study report of 829-12.

ORGAN	Healthy Subjects (n=11) rad/mCi	Diseased Subjects (n=11) rad/mCi	Liver Disease (n=5) rad/mCi	Renal Disease (n=4) rad/mCi	Lung Cancer (n=2) rad/mCi
Adrenals	4.6E-02	4.1E-02	4.3E-02	4.2E-02	3.7E-02
Brain	1.3E-02	1.1E-02	1.1E-02	1.3E-02	7.2E-03
Breasts	2.5E-02	2.4E-02	1.6E-02	4.0E-02	9.6E-03
Gallbladder Wall	3.3E-02	3.6E-02	3.5E-02	3.7E-02	3.3E-02
LLI Wall	1.5E-02	1.3E-02	1.2E-02	1.3E-02	1.2E-02
Small Intestine	2.0E-02	1.7E-02	1.7E-02	1.7E-02	1.6E-02
Stomach	2.1E-02	2.0E-02	2.0E-02	2.0E-02	1.9E-02
ULI Wall	1.9E-02	1.8E-02	1.8E-02	1.8E-02	1.7E-02
Heart Wall	4.7E-02	6.0E-02	5.6E-02	7.0E-02	4.9E-02
Kidneys	3.9E-01	2.8E-01	3.4E-01	2.2E-01	2.4E-01
Liver	6.8E-02	8.9E-02	8.4E-02	1.0E-01	7.5E-02
Lungs	4.8E-02	5.8E-02	5.0E-02	6.5E-02	6.4E-02
Muscle	1.2E-02	1.1E-02	1.1E-02	1.1E-02	1.1E-02
Ovaries	1.7E-02	1.4E-02	1.4E-02	1.4E-02	1.3E-02
Pancreas	3.9E-02	3.6E-02	3.7E-02	3.6E-02	3.3E-02
Red Marrow	8.3E-02	7.2E-02	7.3E-02	7.9E-02	5.8E-02
Bone Surfaces	5.7E-02	5.1E-02	5.1E-02	5.5E-02	4.4E-02
Skin	5.6E-03	5.4E-03	5.0E-03	5.7E-03	5.8E-03
Spleen	1.7E-01	1.4E-01	1.6E-01	1.3E-01	1.3E-01
Testes	1.0E-01	1.2E-01	1.2E-01	1.4E-01	9.9E-02
Thymus	1.1E-02	1.3E-02	1.1E-02	1.4E-02	1.3E-02
Thyroid	8.5E-02	9.2E-02	7.8E-02	1.1E-01	8.6E-02
Urinary Bladder Wall	4.1E-02	2.5E-02	3.4E-02	1.7E-02	1.7E-02
Uterus	4.6E-02	1.6E-02	2.0E-02	1.2E-02	1.2E-02
Total Body	1.9E-02	1.8E-02	1.8E-02	1.9E-02	1.7E-02
Effective Dose Equivalent†	8.4E-02	8.4E-02	8.8E-02	8.2E-02	7.7E-02
Effective Dose†	5.9E-02	6.2E-02	6.4E-02	6.1E-02	5.8E-02

† units of rem/mCi

6-3. REVIEWER'S COMMENTS ON DOSIMETRY

(1) It has been stated that " The total body clearance for all subjects was via the renal pathway (4.2-22.7 %). Hepatobiliary clearance was negligible." However, no supportive data for hepatobiliary clearance were submitted.

(2) Between normal and disease groups, there are noticeable differences of residence time (i.e., biodistribution) in liver, kidneys, and lungs:

The liver residence times are about 51% longer for the disease subjects, and the increase is the largest for the renal patients group (68%).

The kidney residence times are about 29% shorter for the diseased subjects, and the decrease is largest for the renal patients (45%).

The lung residence time for lung patients appeared to be 68 % longer than that of normal subjects (0.62 hours).

Since the liver and kidneys are major eliminating organs and the malignant lung tumor(s) are the target tissue for imaging, these differences should be considered seriously and need to be elucidated from the perspectives of pharmacokinetics and efficacy. Due to the small number of subjects, the statistical analysis of the significance of these differences was not possible at present. It is recommended that the additional study should be conducted for the evaluation of the pharmacokinetics in such target and special populations.

(3) For residence time estimation, the applicant fit the time – activity data to mathematical model. However, neither the model nor the goodness of the fit was provided.

(4) Number of source organ: The 11 organs were studied as radiation source.

(5) The urine collection time in dosimetry analysis (22-31 hours) appeared to be different from the applicants' data in pharmacokinetic analysis (4 hours). There is no individual data of urinary excretion in the dosimetry section.

(6) This reviewer found that the applicant did not provide the dosimetry data obtained from study 829-10. However, in the IND stage, the applicant submitted the dosimetry data from the study report of 829-10 on 10/31/95. Also this reviewer found that the tissue distribution, residence time, and absorbed dose submitted on 10/31/95 are different from the data submitted in study 829-12. The applicant should provide explanation for discrepancies between data submitted on 10/31/95, i.e., dosimetry data from study 829-10 and the study report 829-12; in addition the applicant should provide explanation for not submitting the study 829-10 dosimetry data.

7. OVERALL COMMENTS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-012. From clinical pharmacology and biopharmaceutic perspectives, the present submission did not provide adequate information regarding pharmacokinetics.

The deficiencies may be summarized as follows:

(1) Due to the failure of the collecting samples, limited number of subjects, variation of the data from study to study, and insufficient information on metabolite, the elimination of the Technetium 99m Tc depreotide has not been appropriately elucidated.

(2) The pharmacokinetics of depreotide (peptide moiety) has not been studied.

It should be noted that the pharmacokinetic analyses in both studies , 829-10 and –12, are not for depreotide, but for the radioactivity. Due to the failure of developing the analytical method for depreotide, the applicant could not provide the depreotide disposition data in the body.

(3) The pharmacokinetics in diseased population: Target population (lung cancer patients)

Only two lung cancer patients were studied. Any conclusion is not possible due to the limited number of patients. However, it should be noted that the biodistribution of radioactivity in lung tissue appeared more extensive than that in normal subjects. The lung residence time was 68 % longer in lung cancer patients than that in normal subject. The radiation absorbed dose appeared to be more extensive than the other tissue (Please refer to the dosimetry analysis in this review). Also, the protein binding, volume of distribution, and clearance appeared to be different from the normal values.

(4) The pharmacokinetics in diseased population: Hepatic and renal patients

Three hepatic patients (2 males and 1 female subjects) and 4 renal patients (2 males and 2 females) have been reported. It may be difficult to conclude whether the pharmacokinetics in these patient populations is identical or not with normal subject.
However, it should be noted that the biodistribution data appeared to be different from normal: In hepatic patients, the two tissues appeared to be different in biodistribution of radioactivity more than 30% of the normal value. In renal patients, kidney residence time decreased by 45%, and liver residence time increased by 68%. This may warrant additional studies on the potential differences in disposition of the depreotide.

(5) Pharmacokinetics in special population groups: geriatrics, pediatrics, and nursing mother.

Studies have not been conducted to assess the disposition of Technetium Tc 99m depreotide in geriatrics, pediatrics, and nursing mother.

The applicant reported the correlation of age vs. pharmacokinetic parameters. However, whether the age can affect the pharmacokinetics of the depreotide or not is inconclusive due to the following reason:
The pharmacokinetic parameters from study 829-10 and 829-12 appeared to be different. Therefore, only 9 subjects (4 males and 5 females) from the study 829-12, in which the formulation was treated as the recommended in the proposed package insert, should be used. Due to the gender difference in clearance values, the sample size is too small to evaluate the age

effect on the pharmacokinetics of depreotide. In addition to the number of subjects, the range of age was in between 19-28 years old in the study 829-12. Therefore, it appeared to be inappropriate to test the age effect on the pharmacokinetics of Technetium Tc 99m depreotide.

(6) Dosimetry: The dosimetry results should include the followings:

> For residence time estimation, the applicant fit the time – activity data to mathematical model. However, no data of the mathematical model and the goodness of the fit were provided.
>
> Number of source organ: The 11 organs were studied as radiation source. The applicant needs to explain why other organs were not studied.
>
> The urine collection time appeared to be different from the applicant's data in pharmacokinetic analysis. There is no quantitative and individual data in the dosimetry section. Those data should be provided and the inconsistency needs to be explained by the applicant.

This reviewer found that the applicant did not provide the dosimetry data obtained from study 829-10 that reported on 10/31/95. Also this reviewer found that the tissue distribution, residence time, and absorbed dose submitted on 10/31/95 are different from the data submitted in Study 829-12. The applicant should provide explanation for discrepancies between data submitted on 10/31/95, i.e., dosimetry data from study 829-10 and the study report 829-12; in addition the applicant should provide explanation for not submitting the study 829-10 dosimetry data.

8. LABELING COMMENTS

The labeling Comments will be covered under a separate review.

APPEARS THIS WAY
ON ORIGINAL

9. COMMENTS TO THE APPLICANT

The applicant is encouraged to conduct pharmacokinetic studies to obtain the following information:

(1) Elimination characteristics of Neotech ™.
Due to the failure of the collecting certain samples, limited number of subjects, and insufficient information on metabolite, the elimination of the Technetium 99m Tc depreotide has not been appropriately elucidated. Please provide appopriate information on the elimination characteristics of Neotech ™.

(2) The pharmacokinetics information of depreotide (peptide moiety).

The pharmacokinetic analyses in both studies , 829-10 and –12, are not for depreotide, but for the radioactivity. Please provide appropriate pharmacokinetic information on the peptide ligand.

(3) The pharmacokinetics of Neotech ™ in target population.

In the present submission, the two lung cancer patients were studied. Any conclusion is not possible due to the limited number of samples. Please obtain pharmacokinetics of Neotech ™ in lung patients.

(4) The pharmacokinetics of Neotech ™ in geriatric and pediatric population.

The applicant lacks Neotech ™ pharmacokinetic information in geriatric and pediatric population. Please obtain pharmacokinetics of Neotech ™ in these populations.

(5) It appears that pharmacokinetic parameters obtained from Study 829-10 differs from that of Study 829-12. Please explain.

(6) The applicant did not provide dosimetry information obtained from Study 829-10 in the current NDA, although this information was submitted in the IND (Submission date 10/31/95). Please explain.

(7) Please address the feasibility of obtaining pharmacokinetics of Neotech ™ in renally and hepatically impaired patients. It seems that Neotech ™ is eliminated in both renal and hepatic routes.

(8) Please conduct gender analysis as appropriate.

The applicant should submit pharmacokinetic study protocols to the agency prior to conducting studies for the agency's comment.

APPENDIX

APPEARS THIS WAY
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Appendix –1. SUMMARY OF INDIVIDUAL STUDIES

Appendix 1-1. PHASE I PHARMACOKINETIC STUDY IN NORMAL VOLUNTEERS (STUDY NO. 829-10)

Protocol deviations:

(1) Failure to record measurement times for vital signs for all subjects
(2) Failure to obtain blood and urine clearance data and whole body imaging data for Subjects 829-10-02-06 and –07
(3) Failure to record P829 peptide dose for Subjects 829-10-02-06 and –07.

Title of study:
Phase I clinical trial evaluating the safety and tolerance of Technetium Tc 99m P829 in the detection and localization of somatostatin receptor-expressing tumors in normal volunteers

Investigators:

Study Centers:

Study Period:
8/21/95 – 2/29/96

Objectives:
To evaluate Technitium Tc 99m P829 for its: (1) overall safety and tolerance in human subjects, and (2) biodistribution, uptake and clearance, half-times, and routes of elimination in normal volunteers in order to determine human dosimetry and pharmacokinetics.

Study Design:
Nonrandomized, unblended clinical trial.

Number of Subjects:
Initially planned 10-15, 17 enrolled, 17 analyzed and 15 reported for pharmacokinetics and biodistribution.

Inclusion criteria:
(1) Give written informed consent to participate in the study
(2) Be over 18 years of age
(3) Be male or female, Females may not be pregnant or lactating, and those of childbearing potential must have had a current negative pregnancy test.
(4) Be a normal with medical history and current physical examination indicating good health.
(5) Have current stable vital signs and baseline blood and urine laboratory test drawn in accordance with the study schedule.

Dose:
Doses of the study agent were prepared from nonradioactive kits [redacted]

Each subject received a single intravenous injection of approximately 50 µg P829 peptide labeled with approximately 10 mCi Technitium 99m.

Efficacy:
Efficacy was not assessed in this study.

Pharmacokinetics:
Blood samples were collected at multiple time points (Please see Table), and urine was collected for 24 hours post-injection, to monitor radioactivity in the body.

Biodistribution:
Serial whole body imaging (gamma scintigraphy) was performed at multiple time points post-injection to determine the biodistribution.

Safety:
Safety was monitored by periodic assessment of vital signs and clinical laboratory rests. Questionnaires were completed by each subject at baseline and at 4 hours and 18-24 hours post injection to help document any adverse events.

Results:

Pharmacokinetic results:
Blood radioactivity levels following Technetium Tc 99m P829 administration exhibited triphasic decay, with a rapid decline in radioactivity soon after administration (median half-life 3.7 min), followed by a more gradual decline with a half-life of 35.2 min, and a slow decline with a half-life of 17.9 hour (median values). The median values of body weight normalized Vss and CL were 3.12 L/kg and 3.89 ml/min/kg, respectively. Urinary excretion accounted for 5.3 – 7.7 % of the total dose, and average renal clearance (CLr) was 0.255 ml/min/kg (less than 10 % of the total clearance). Statistical analysis did not indicate any consistent effects of demographic characteristics such as gender, age, and weight on pharmacokinetic parameters, and no perceivable trends were present in plots of Vss and clearance versus age.

Biodistribution Results:
Ten minutes post-injection, the highest activities were in the kidney (13.01% of injected dose), liver (10.54%), pelvic area(6.29 %). During the first 24 hours post-injection, activity remained nearly constant in these regions.

Safety results:
No adverse events related to the administration of the study agent were reported. Changes in vital signs and clinical laboratory tests were transient and not clinically significant.

Conclusions:

(1) Blood radioactivity levels for Technitium Tc 99m P829 exhibited triphasic decay. The first two phases had half-lives on the order of minutes, while the third phase had a median half-life of 17.9 hours.
(2) Estimates of Vss suggested that there was significant distribution into body tissues.
(3) Urinary excretion of Technetium Tc 99m P829 accounted for 5.3-7.7 % of the total dose.
(4) Ten minutes after injection, radioactivity was greatest in the kidney, liver, pelvic area, and lungs; and during the first 24 hours post-injection, activity remained nearly constant in these regions.
(5) This dose appeared to be safe and well tolerated.

Appendix 1-2. PHARMACOKINETIC STUDY IN NORMAL VOLUNTEERS AND PATIENTS (STUDY NO. 829-12)

Protocol Deviations:

(1) Failure to complete Technetium Tc 99m P 829 imaging and safety assessments for subject 829-12-01 due to camera malfunction
(2) Failure to record vital signs at 24 hours post-injection for subject 829-12-03
(3) Failure to record vital signs at 60 min post-injection for subject 829-12-07
(4) Failure to complete vital signs for subject 829-12-19
(5) Baseline urine test positive for tetrahydrocarabinol for subject 829-12-14
(6) Baseline urine test positive for opiates for subject 829-12-19, and 23
(7) No fecal samples were collected.
(8) No 12 hour blood samples for pharmacokinetic analysis were collected.
(9) Laboratory tests were performed at 4 hours post injection, not 3 hour post-injection as protocol.

Subjects: five of the planned six patients with hepatic dysfunction were enrolled; four of the planned six patients with renal dysfunction were enrolled; two of the planned six patients with lung cancer were enrolled; and zero of the planned six patients with neuroendocrine tumors were enrolled.

Title of the Study:
A single center clinical study to evaluate the pharmacokinetics, radiation dosimetry and safety of Tc 99m P829 in normal volunteers and patients.

Investigator:

Study Center:

Objectives:
To evaluate (1) the safety of Technitium Tc 99m P829 in normal volunteers and patients displaying evidence of renal or hepatic functional impairment, or having neoplastic disease, (2) the pharmacokinetics and radiation dosimetry of Technetium Tc 99m P829 in these subjects. Pharmacokinetic parameters to be evaluated included distribution, metabolism and excretion, and (3) the pharmacokinetics of unlabeled P829 (i.e., the immunoreactive core peptide) in these subjects.

Design:
Non-randomized, open-label clinical trial.

Subjects:
Planned- up to 30; Enrolled –23; Analyzed- 23 for safety, 19 for pharmacokinetics (17 data were used for recommended package insert), 5 for renal clearance, 22 for dosimetry, plasma protein binding and plasma [redacted] 21 for urine [redacted]

Inclusion criteria:
(1) 18 years or older
(2) Written informed consent obtained prior to initiation of any protocol specified procedure.
(3) Normal volunteers or patients (in-or out patients) satisfying above criteria and
(4) Patients could have renal or hepatic dysfunction, or cancer of the lung.

Dose:
Doses of the study agent were prepared from nonradioactive kits. [redacted]
Each subject received a single intravenous injection of approximately 50 μg P829 peptide labeled with approximately 15-20 mCi Technitium 99m.

Pharmacokinetic evaluation:
Blood samples were collected at multiple time points post-injection, and urine was collected for 24 hours post injection to monitor radioactivity in the body.

Biodistribution:
Serial whole body imaging (gamma scintigraphy) was performed at multiple time points post-injection to determine the biodistribution.

Immunogenicity:
Baseline and 3-week plasma samples from 9 normal subjects were tested for the presence of IgM and IgG antibodies to P829.

Safety:
Safety was monitored by periodic assessment of vital signs and clinical laboratory tests.

Statistical method:
For pharmacokinetics, tri-exponential functions were fitted to the plasma total radioactivity concentration versus time profile. Pharmacokinetic parameters derived from the tri-exponential functions include AUC, terminal elimination rate constant, half-life, Vss, CL, and CLr. The pharmacokinetic parameters in individual subjects were summarized. The pharmacokinetic parameters were summarized for males and females separately, and both sexes combined. The data were also summarized separately for healthy subject and patients with hepatic and renal dysfunction, and those with lung cancer. The effect of demographic characteristics (gender, age, and weight) on the pharmacokinetic parameters for Tc 99m P829 (total radioactivity) were examined using following statistical model:
Response= mean+ gender + age + weight + error
Where gender was a class variable and age and weight were continuous

Plasma protein binding:
The fraction of P829 bound to plasma proteins was estimated using the following formula:
% bound= [net cpm in filtrate/ net cpm in unfiltered plasma] x 100

Biodistribution data:
The mean and individual amount versus time curves were plotted on linear and semi log scale for selected regions of interest. The data were analyzed by the [redacted] to estimate the organ residence time and radiation absorbed dose.

Safety data:
Laboratory values outside the normal range for each parameter assessed were identified and flagged as abnormals or high abnormals. Laboratory values at each assessment time were summarized using descriptive statistics. Change from baseline by type of patient was summarized for the following parameter: ALT, AST, alkaline phosphatase, total bililubin, GGT, BUN, and creatinine.

Pharmacokinetics results:
Total radioactivity in plasma was almost exclusively associated with P829. Systemic clearance was 155 ml and renal clearance was 23 ml/min. The relatively low renal clearance indicated extra-renal elimination. Volume of distribution was 114 L. Plasma protein binding was 12 %. There were gender difference in clearance : clearance in female subjects appear to be lower than that in male subjects.

Biodistribution:
The highest activities were in the live and kidney (7 – 15 % of injected dose). Tissue distribution in disease states appeared to be different from those in healthy subject for liver and kidneys.

Immunogenicity:
Technetium Tc 99m P829 injection did not generate human IgM or IgG in the present experiment.

Safety:
No adverse events related to the administration of the study agent reported.

Conclusion:
(1) P829 was characterized a drug of low protein binding, low systemic clearance and large volume of distribution and a terminal half-life of 20 hours. The difference of pharmacokinetics of P829 in renally, hepatically-impaired patients, or in patients in lung cancer, appeared to be inconclusive based on the current study since only limited number of patients had been studied.
(2) The highest activities were in the live and kidney (7 – 15 % of injected dose). Tissue distribution in disease states appeared to be different from those in healthy subject for liver and kidneys.
(3) There was no generation of P829 specific antibodies.
(4) This dose was safe and well tolerated.

Appendix 1-3. PHARMACODYNAMIC STUDY IN NORMAL VOLUNTEERS (STUDY NO. 829-13)

Title of the study:
A single center clinical study to evaluate the pharmacodynamics of P829 in normal human volunteers.

Investigator:

Study Center:

Objectives:
(1) To evaluate the pharmacodynamic effects of P829 and octreotide on the glucose tolerance response in normal volunteers, and
(2) To evaluate the potential generation of antibodies to P829 in normal volunteers following in vivo exposure to clinical doses of P829 and octreotide.

Subjects:
Planned, enrolled and analyzed 9 .

Inclusion criteria:
(1) Healthy male or female over the age of 18 years and within ±20 % of ideal body weight.
(2) If female, have been post menopausal or surgically sterile and had a negative serum pregnancy test 24 hours prior to receiving study medication. If not, must have been using intrauterine device, double barrier or hormonal (birth control pills) method of contraception, non-lactating, and had a negative serum pregnancy test within 24 hours of receiving study medication.
(3) Good general health as determined by medical history, physical examination, blood, and urine laboratory test.
(4) Not chewing or smoking tobacco 12 hours prior to dose and until 6 hours after receiving the dose.
(5) Must have been willing and able to sign and date the informed consent form and follow study procedures
(6) Must test negative urine drug and alcohol test results, and
(7) Have clinical laboratory test results that are within normal limits during the screening visit, or if abnormal, are not deemed clinically significant by the investigator.

Dose:
Doses of the study agent were prepared from nonradioactive kits.

Each subject received a single intravenous injection of approximately 50 µg P829 peptide.

Duration of treatment:
On Days 0, 4, and 8 each subject received either: a single intravenous injection of P829, or octreotide of no peptide injection followed by oral glucose beverage.

Pharmacodynamics:
Glucose tolerance test (GTT) to evaluate the effect of P829 and octreotide on the glucose response.
Descriptive statistics of the change from baseline at each timepoint in the GTT response for P829, octreotide, and no peptide were tabulated. Glucose tolerance curves were presented for all subjects and for each dosage group.

Immunogenicity:
Baseline serum samples and 3-week post injection serum samples were collected to evaluate the presence of P829 specific antibodies.

Safety:
Safety was assessed through the monitoring of adverse events, vital signs, and clinical laboratory tests.

Summary and Conclusion:
P829 treatment did not alter the physiological response to a glucose challenge, as the GTT curve for P829 was similar to the baseline curve. The GTT curve for octreotide treatment showed a significant but transient rise in serum glucose level.
P829 treatment did not lead to the generation of human P829 specific antibodies.

APPENDIX 1-4. IN VITRO EVALUATION OF THE COMPATIBILITY OF 99M TC DEPREOTIDE INJECTION REPARED WITH DECAYED GENERATOR ELUTE WITH HUMNA BLOOD OR SERUM.

Summary

Technetium Tc 99m P829 injection is recommended to be administered as a bolus injection. At the close to the site of injection, the blood is exposed to high concentrations of the injected material immediately after its bolus administration.
Therefore, the sponsor studied if hematological change would occur during bolus intravenous injection.

Human whole blood and serum obtained from one male and one female were exposed in vitro to dosing solutions of Technitium Tc 99m P 829 Injection prepared with decayed generator elute in ratios of 4:1 or 8:1. These ratios approximate the instantaneous concentration of an injection of 1 ml of injection over 10 seconds into the antecubital vein with a flow of 90 ml/min.

There was no observable effect of injected solution on hematological parameters. In the vehicle control of the female subject at 1:4 dilution to blood, Rouleaux formation was noted. However, it was not evident in the parallel treated 1:4 dilution sample. The degree of Rouleaux formation was not considered to be large enough to confound interpretation of the result.

There was no evidence of hemolysis, Hgb changes, or decrease RBC counts, nor was there evidence of protein precipitation. All parameters remained within normal limits and within expected effects from dilution alone.

Reviewer's Comment

Based on the discussion with the reviewing medical officer, the experiment appeared to be adequate and this reviewer is of the opinion that the injection manner is safe with the recommended dose.

APPENDIX 1-5. DISTRIBUTION OF 99M TC DEPREOTIDE BETWEEN HUMAN BLOOD COMPONENTS IN VITRO.

Summary

The purpose of this study was to evaluate the distribution of Technitium Tc 99m P 829 between cellular components and plasma proteins of human blood.

Technitium Tc 99m P829 injection was added to citrated human blood in a final concentration of 10 nM. Blood spiked with Technitium Tc 99m P829 was fractionated into mononuclear white cells (lymphocytes and monocytes), polymorphonuclear leukocytes (PMN), erythrocytes and plasma by density gradient centrifugation using a ficoll-based medium. Since plates are not isolated by this procedure, other method was used to isolate platelets from other blood cells. Citrated blood was fractionated into platelet-rich (PRP) and platelet-poor-plasma (PPP) by sequential slow and high speed centrifugation, respectively.

Over 98 % of Technitium Tc 99m P 829 was free in plasma, with less than 1 % associated with platelets, white blood cells, or red blood cells.

Gel filtration chromatography revealed that less than 2 % of Technetium Tc 99m P829 binds to plasma proteins.

Reviewer's Comment

The low protein binding (less than 2 %) in vitro seems to be comparable with the low in vivo plasma protein binding (12 %) results. The low binding to blood cells and plasma protein binding also consistent with the observation that Technitium Tc 99m P829 disappears from the blood rapidly with distribution half-life of 5 min.

Appendix –2. APPLICANT LABELING

APPEARS THIS WAY
ON ORIGINAL

17 pages Redacted

DRAFT LABELING