Subgroup Analysis: This analysis used the patient-based aggregate reader agreement rates.

Patients presenting with primary lung cancer: Twenty patients presented with suspicion of tumor of the lung. Of the 20, 18 were found to have a positive final institutional clinical diagnosis versus 2 who were found not to have lung cancer by final institutional clinical diagnosis (Table 17). No significant difference in agreement rates between the blinded readers and the final institutional diagnosis was seen between the two modalities.

Table 17. A COMPARISON OF P829 AND OCTREOSCAN IN PATIENTS FOR WHOM PRESENTING DIAGNOSIS WAS CONFIRMED OR SUSPECTED LUNG CANCER

			Agreement @ (N / %)		
Final Diagnosis	N	Reader	P829	Octreo	p-value
POS	17	1	14 (82)	14 (82)	0.617
	18	2	15 (83)	15 (83)	0.479
	18	3	15 (83)	15 (83)	0.617
	18	AGG.	14 (78)	16 (89)	0.617
	18	INV.	17 (94)	17 (94)	--
NEG	2	1	1 (50)	2 (100)	1.000
		2	0	2 (100)	0.479
		3	0	1 (50)	1.000
		AGG.	0	2 (100)	0.479
		INV.	0	2 (100)	0.479

@ Agreement for patients for whom final diagnosis = POS corresponds to sensitivity; agreement for patients for whom final diagnosis = NEG corresponds to specificity. POS = positive for tumor, NEG = negative for tumor, AGG = Aggregate blind read and INV = Investigator's reading.
Data Source: Sponsor Test Table XXVIa, Vol. 1.50, page 079.

Age: The agreement rate for In-111 pentetreotide was statically significantly better than that for Tc99m P829 when compared to the final institutional diagnosis for patients under the age of 65 years ($p < 0.001$) and for patients above the age of 65 years ($p < 0.05$).

Gender: The agreement rate for In-111 pentetreotide was statically significantly better than that for Tc99m P829 when compared to the final institutional diagnosis for both male and female patients.

Race: The agreement rate for In-111 pentetreotide was statically significantly better than that for Tc99m P829 when compared to the final institutional diagnosis for Caucasian patients.

Patients with Abnormal Renal and Liver Function: Thirteen evaluable patients (10%) had abnormal renal function and 54 evaluable patients (42%) had abnormal liver function. The agreement rate of Technetium Tc 99m P829 results with final institutional clinical diagnosis was lower than the corresponding agreement rate of indium In 111 pentetreotide results for both subgroups (normal and abnormal) defined by renal function and for both subgroups (normal and abnormal) defined by liver function.

Sponsor's efficacy conclusions:

The primary efficacy indicator of this study was the patient-based agreement rate of Technetium Tc 99m P829 images with final institutional clinical diagnosis compared with the patient-based agreement rate of indium In 111 pentetreotide images. Indium In 111 pentetreotide results were used as, or contributed to, the final institutional clinical diagnosis. Under these conditions, Technetium Tc 99m P829 is not as effective as indium In 111 pentetreotide in detecting and localizing somatostatin-receptor expressing neuroendocrine tumors. The agreement rates of Technetium Tc 99m P829 with final institutional clinical diagnosis for the three blinded readers ranged from 51.6 to 56.6%. The agreement rates for indium In 111 pentetreotide with final institutional clinical diagnosis for the three blinded readers ranged from 73.8 to 78.7%.

Two explanations for the superior performance of indium In 111 pentetreotide became evident during the study. First, indium In 111 pentetreotide was used as a diagnostic modality for determining the final institutional clinical diagnosis in 95% of evaluable patients. Consequently, blinded reads of indium In 111 pentetreotide images were compared with final institutional clinical diagnosis that used unblinded reads of indium In 111 pentetreotide images in most cases. This circumstance created a bias in favor of the higher agreement rate that was observed for indium In 111 pentetreotide.

A second explanation for the superior performance of indium In 111 pentetreotide concerns problems with imaging the abdomen shortly after administration of Technetium Tc 99m P829. Imaging with Technetium Tc 99m P829 was performed before the non-specific uptake in abdominal structures had time to clear, and the visualization of tumor may have been occluded by background uptake. Imaging with indium In 111 pentetreotide is typically done at least 24 hours post-injection, which allows sufficient time to permit clearance from the abdomen.

This explanation is supported by the region analyses. Agreement rates of Technetium Tc99m P829 images with final institutional clinical diagnosis were comparable to agreement rates of indium In 111 pentetreotide images with final institutional clinical diagnosis for the head/neck and the chest regions, but agreement rates of technetium Tc99m P829 images with final institutional clinical diagnosis were significantly lower than agreement rates of indium In 111 pentetreotide images with final institutional clinical diagnosis for the abdomen.

The differences in sensitivity between the two agents, 45.2% for Technetium Tc 99m P829 and 71.8% for indium In 111 pentetreotide images were similar to the differences for agreement rate, but specificity of technetium Tc99m P829 results, 71.4% was comparable to specificity of indium In 111 pentetreotide results, 76.2%.

Site investigator evaluations of Technetium Tc 99m P829 relative to final institutional clinical diagnosis yielded a 69% agreement rate, which is markedly higher than the blinded reader evaluations of Technetium Tc 99m P829 images with final institutional clinical diagnosis, though still significantly lower than the site investigator evaluations of indium In 111 pentetreotide images relative to final institutional clinical diagnosis. Agreement rates for the chest were similar for Technetium Tc99m P829 (90%) and indium In 111 pentetreotide (97%) and, like the blinded reader evaluations, agreement rates for the abdomen were noticeably higher for indium In 111 pentetreotide (92%) than for Technetium Tc99m P829 (74%).

These data demonstrate that while technetium Tc 99m P829 images are not comparable to indium In 111 pentetreotide images for ht abdomen, efficacy of technetium Tc 99m P829 for detecting and localizing somatostatin-receptor expressing neuroendocrine tumors in the thoracic cavity is comparable to the efficacy of indium In 111 pentetreotide imaging.

Safety: The safety data was not divided and analyzed by dose preparation (heated and unheated), therefore, only adverse events will be reviewed. The safety of the heated dose preparation cannot be adequately addressed given the Sponsor's presentation of the data.

Deaths: 0
Withdrawals due to an Adverse Event: 0
Serious Adverse Events: 0
Severe Adverse Events: 0

Extent of Exposure: A total of 135 patients received a single intravenous administration of Tc99m P829. The radioactive dose was ranged from 10.9 to 26.9 mCi and the peptide dose ranged from 12.5 to 50 μg. The lots used in this study include 9509B01B and D, 9509M01B, 9609B01B and 9609B02B. A total of 99 patients received the heated dose preparation and 36 received the unheated dose preparation.

Adverse Events: Five patients experienced 8 adverse events. All adverse events were mild in severity and were all self-limiting. Only one adverse event, vasodilatation, was considered as possibly related to study drug. All patients experiencing adverse events were noted to have abnormal baseline liver function tests. No deaths or serious adverse events occurred during the study.

Table 18. Adverse Events

Patient	Event	COSTART Term	Severity	Onset post Injection	Duration	Treatment	Related to Drug
1-5	Nausea and vomiting	Nausea and vomiting	Mild	92 min.	23 min.	No	Probably not related
1-13	Nausea	Nausea	Mild	16 hr.	2 hr.	No	Probably not related
1-20	Increased Blood Pressure	Hypertension	Mild	59 min.	NR	No	Probably not related
	Increased Blood Pressure	Hypertension	Mild	3 hr.	NR	No	Probably not related
4-1	Headache	Headache	Mild	30 min.	30 min	No	Probably not related
	Tired	Asthenia	Mild	30 min	NR	No	Probably not related
4-6	Dizziness/ lightheaded	Dizziness	Mild	75 min.	4 hr.	No	Probably not related
	Flushing	Vasodilatation	Mild	5 hr.	5 min.	No	Possibly

Data Source: Vol. 55, pg. 109. NR= Not recorded

Comment: Those patients that are bolded in the table above represent those who received the unheated dose preparation.
***Patient 1-20** had an elevation in systolic and diastolic blood pressure at the 60 minute and 3- hr. assessments. Baseline systolic pressure was 106 mmHg and rose to 142 and 140 mmHg for the 60minute and 3-6 hr. assessment respectively. Diastolic baseline pressure was 60mmHg and rose to 90 and 92 mmHg for the 60 minute and 3-6 hr. assessments respectively. Both systolic and diastolic pressures fell at the 24 hour assessment to values below baseline. Pulse and respiratory rate were stable.*

No dramatic vital sign shifts were seen for any of the other patients who experienced an adverse event.

Laboratory Data:

The following changes in laboratory measurements from baseline values were to be considered clinically significant (with the exception of WBC differential) by the Sponsor:

i. Baseline within normal range, post-injection value out of normal range and at least a 25% change from baseline.

ii. Baseline out of normal range (high or low), post-injection value still out of range in the same direction with a 25% further increase or decrease from baseline.

iii. Baseline missing, post-injection value out of normal range.

Sponsor's safety Conclusions: Safety was assessed by laboratory tests, vital signs, and occurrence of adverse events during the 1st hour, at 2–4 hours, and again at approximately 24 (18–30) hours after the injection of technetium Tc 99m P829. No changes were seen in these parameters that were attributed by the investigators to be caused by the study drug. Based on these data, technetium Tc 99m P829 appeared to be safe when administered as a single intravenous dose of 50 μg containing15–20 mCi to adult patients with malignant melanoma.

Reviewer's Conclusions:
Efficacy: Since this study does not address lung tumor detection as proposed as the drugs indication, this study was not reviewed for efficacy purposes. The Sponsor's results were reported, however.

Safety: No significant trends in vital sign and laboratory data were identified in these patients presenting with melanoma.

12.0 Pharmacoeconomic Analysis

A pharmacoeconomic assessment of the clinical utility of Tc99m P829 in the evaluation of solitary pulmonary nodules (SPN) was performed as a post hoc analysis. Given the problems seen with improper designation of patients with SPN and the fact that this was not formally studied and supported by an epidemiological study and not considered as part of the Sponsor's marketing claims, this data was not reviewed.

APPENDIX A
Lung Tumor Staging Criteria - Study P829-30/IIa

TABLE 17

LUNG

Data Form for Cancer Staging

Patient identification
Name
Address
Hospital or clinic number
Age ___ Sex ___ Race

Institution identification
Hospital or clinic
Address

Oncology Record

Anatomic site of cancer
Histologic type
Grade (G)
Date of classification

Clin	Path
[ ]	[ ]
[ ]	[ ]
[ ]	[ ]
[ ]	[ ]
[ ]	[ ]
[ ]	[ ]
[ ]	[ ]
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DEFINITIONS

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumor

Tis Carcinoma *in situ*

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus* (i.e., not in main bronchus)

T2 Tumor with any of the following features of size or extent:
- More than 3 cm in greatest dimension
- Involves main bronchus, 2 cm or more distal to the carina
- Invades the visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; separate tumor nodule(s) in the same lobe; or tumor with a malignant pleural effusion**

* *The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.*

** *Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is nonbloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3.*

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor

N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s).

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis present (includes synchronous separate nodule[s] in a different lobe)

(continued on next page)

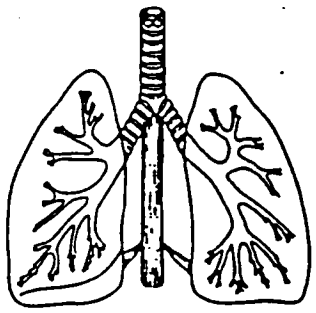
Clin	Path	Stage Grouping			
[ ]	[ ]	Occult	TX	N0	M0
[ ]	[ ]	0	Tis	N0	M0
[ ]	[ ]	IA	T1	N0	M0
[ ]	[ ]	IB	T2	N0	M0
[ ]	[ ]	IIA	T1	N1	M0
[ ]	[ ]	IIB	T2	N1	M0
			T3	N0	M0
[ ]	[ ]	IIIA	T1	N2	M0
			T2	N2	M0
			T3	N1	M0
			T3	N2	M0
[ ]	[ ]	IIIB	Any T	N3	M0
			T4	Any N	M0
[ ]	[ ]	IV	Any T	Any N	M1

Staged by _____ M.D.

_____ Registrar

Date _____

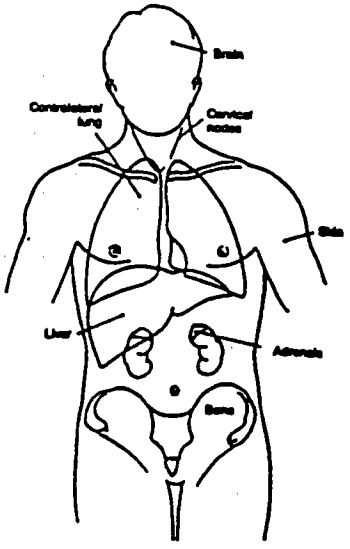
Illustrations



Show primary tumor, indicating size in cm (greatest diameter) and measurability:

EV = evaluable
ME = measurable
NE = nonevaluable

Show lymph node metastases.



Distant metastases beyond hemithorax. Indicate all known metastases.

Histopathologic Grade (G)

[ ] GX Grade cannot be assessed
[ ] G1 Well differentiated
[ ] G2 Moderately differentiated
[ ] G3 Poorly differentiated
[ ] G4 Undifferentiated

Lymph Nodes

Mediastinal:
- Peritracheal (including those that may be designated tracheobronchial, e.g., lower peritracheal, including azygos)
- Pretracheal and retrotracheal (including precarinal)
- Aortic (including subaortic, aorticopulmonary window, and periaortic, including ascending aorta or phrenic)
- Subcarinal
- Periesophageal
- Pulmonary ligament

Intrapulmonary:
- Hilar (proximal lobar)
- Peribronchial
- Intrapulmonary (including interlobar, lobar, segmental)

Histopathologic Type

There are four common types of lung cancer

Squamous cell carcinoma (epidermoid carcinoma)
- Variant: Spindle cell

Small cell carcinoma
- Oat cell carcinoma
- Intermediate cell type
- Combined oat cell carcinoma

Adenocarcinoma
- Acinar adenocarcinoma
- Papillary adenocarcinoma
- Bronchiolo-alveolar carcinoma
- Solid carcinoma with mucus formation

Large cell carcinoma
- Variants: Giant cell carcinoma
  Clear cell carcinoma

This classification applies only to carcinomas, including small cell carcinoma. The classification may be applied to those tumors classified as "undifferentiated carcinomas" with no special cell types identified. Sarcomas and other rare tumors are excluded because the relationship between disease extent and prognosis has not been established or does not pertain.

(continued on next page)

APPENDIX B

Staging Analysis- Pivotal Studies

A secondary analysis was to be performed to assess the potential usefulness of Technetium Tc 99m P829 in detecting the spread of primary lung cancer and providing insights into staging. This analysis will compare the American Joint Committee on Cancer (AJCC) lung cancer stage, as provided by the investigator, with the stage derived from the blinded read (hereafter referred to as the BR Stage) for the main presenting lesion for each patient. The BR Stage will be computer-calculated analytically from the results of the blinded read assessment of the Technetium Tc 99m P829 uptake in the nine anatomic regions. The BR Stage will not rely on chest X-ray, CT, or other clinical information that would be used for formal staging. This analysis will include only patients that have a diagnosis of primary lung cancer based on the histopathologic information obtained on the case report form.

The AJCC stage for each patient will be determined by the TNM classification indicated in the CRF section titled "Histopathologic Information" by the investigator. In accordance with the *American Joint Committee on Cancer: Manual for Staging of Cancer* [24], the TNM classification was grouped into stages.

The BR Stage will be obtained for each patient from the Technetium Tc 99m P829 blinded read results as indicated by the decision tree. The first step in the decision tree will be to manually review the blinded read comments for any indication of distant metastases that would indicate Stage IV disease. These patients will be flagged as Stage IV. The remaining patients will be assigned a stage based on the decision tree algorithm.

The AJCC stage based on the histopathology diagnosis will then be compared to the BR stage. For the comparison, Stage 0 and Stage I will be grouped together.

APPENDIX C

Estimates of Bmax and Kd for Receptor Assays - Study 34A

Table 1. Estimated Bmax and K_d Values of Human Tumor Samples*.

Tumor Types	Site-Patient Number	Bmax (high affinity)	K_d
Adenocarcinoma	A1-16	Not Detectable	nd[4]
Adenocarcinoma	A1-15	Not Detectable	nd[4]
Adenocarcinoma	A5-01	590 fmol/mg	12 nM
Adenocarcinoma	A5-08	8 fmol/mg 110 fmol/mg[2]	0.3 nM 6 nM
Adenocarcinoma	A5-13	5 fmol/mg 310 fmol/mg[1]	2.4 nM nd
Squamous Cell	A1-25	Not Detectable	nd[4]
Squamous Cell	A12-02	Not Detectable	nd[4]
Squamous Cell	A5-06	44.3 fmol/mg	0.55 nM
Squamous Cell	A5-02	91 fmol/mg	2.6 nM
Squamous Cell	A5-11	5 fmol/mg[3]	nd
Squamous Cell	A1-32 (Tumor)	56.5 fmol/mg	nd
	A1-32 (Lymph node)	30 fmol/mg 280 fmol/mg[2]	2 nM nd
	A1-32 (Surrounding lung tissue)	Not detectable	nd
Squamous Cell	A5-15	18.4 fmol/mg	nd
Large Cell	A12-15	184 fmol/mg[2]	> 10 nM
Breast	2-91	45 fmol/mg 339 fmol/mg[2]	1.6 nM nd
Granuloma	A8-01 (Inguinal node)	30 fmol/mg 368 fmol/mg[1]	1.8 nM 12 nM
	A8-01 (Lung mass)	57 fmol/mg 339 fmol/mg[2]	6 nM nd

1 Site density at 30 nM Technetium Tc 99m suggesting a second set of binding sites. Bmax and K_d values were estimated from partial saturation curves.

2 Site density at 30 nM Technetium Tc-99m indicative of a second class of binding sites with lower affinity than 10 nM dissociation constant. Saturation was not evident so the K_d of this class of binding sites was not determined and the receptor site density of this population may be higher than the concentration observed at 30 nM Technetium Tc 99m P829 (highest concentration used in this experiment).

3 Single point at 1 nM.

4 Not done

* A = Patients from 829-34A. Patient 2-91 is from 829-22.

Table 2. The Specific Binding of ^{125}I-Somatostatin to Human Tumor Membranes: Summary of Specific Inhibition Studies

Tumor Type	Site-Patient Number	Somatostatin-14	Somatostatin-28	P875 Inhibition	% SSTR Bound by P875
Adenocarcinoma	A1-16	Not detectable	+	Not detectable	
Adenocarcinoma	A1-15	+	+	+	100%
Adenocarcinoma	A5-01	+	+	Not detectable	
Adenocarcinoma	A5-08	+	+	+	100%
Adenocarcinoma	A5-13	+	+	+	100%
Squamous Cell	A1-25	+	Not detectable	+	75%
Squamous Cell	A12-02	+	Not detectable	+	100%
Squamous Cell	A5-06	+	+	+	75%
Squamous Cell	A5-02	+	+	+	100%
Squamous Cell	A5-11	+	nd	nd	
Squamous Cell	A1-32 (Tumor)	+	nd	nd	
	A1-32 (Lymph node)	+	nd	nd	
	A1-32 (Surrounding lung tissue)	+	+	+	57%
Squamous Cell	A5-15	Not detectable	+	+	100%
Large Cell	A12-15	+	+	+	100%
Breast	2-91	+	+	Not detectable	
Granuloma	A8-01 (Lung mass)	+	Not detectable	+	100%
	A8-01 (Inguinal node)	+	nd[1]	nd	

1 Not done

* A = Patients from 829-34A. Patient 2-91 is from 829-22.

The specific binding of ^{125}I-somatostatin-14 in the absence and presence of 500 nM somatostatin-14, somatostatin-28 and P875 (the oxorhenium complex of P829) are shown in Table 2. In some cases, there was only enough membrane protein for the somatostatin-14 inhibition.

APPENDIX D
Patients exposed to study agent more than once.

TABLE 4.3.0

OVERALL EXTENT OF EXPOSURE TO STUDY AGENT
SAFETY POPULATION
PATIENTS EXPOSED TO STUDY AGENT MORE THAN ONCE

Study	Patient ID (Prior ID)	Treatment Date / Time	Actual Dose (ug) P829 Administered	Actual Dose (mCi) Tc 99m Administered
829-20	20-05-04	22MAY95 / 13:55	20.0	9.29
	(20-05-01)	11MAY95 / 10:00	50.0	11.40
829-22	22-02-30	30MAY96 / 9:35	20.0	13.39
	(22-02-23)	17JAN96 / 13:30	20.0	14.00
	22-02-64	31MAR97 / 13:00	15.0	20.34
	(22-02-15)	07AUG95 / 13:45	5.0	10.00
	22-02-66	01APR97 / 09:45	15.0	15.67
	(22-02-44)	25NOV96 / 11:50	16.3	19.87
	22-02-78	27MAY97 / 13:50	15.0	17.96
	(22-02-38)	04OCT96 / 11:40	30.0	16.80
	22-02-80	08JUL97 / 08:45	16.4	19.27
	(22-02-67)	01APR97 / 12:55	15.0	19.24
	22-02-83	01AUG97 / 09:00	15.2	16.67
	(22-02-77)	27MAY97 / 11:25	14.9	16.69
	(22-02-60)	17MAR97 / 11:40	16.4	16.81
	22-02-84	28AUG97 / 13:30	15.0	18.24
	(22-02-47)	20DEC96 / 13:50	15.9	18.19
	22-02-87	23SEP97 / 10:35	15.8	19.39
	(22-02-52)	31JAN97 / 09:15	15.0	18.33
	22-02-91	15OCT97 / 13:05	16.0	19.20
	(22-02-74)	30APR97 / 09:40	17.2	18.01
	22-02-92	13NOV97 / 09:05	15.0	18.82
	(34A-01-32)	24OCT97 / 08:10	50.0	19.40

TABLE 4.3.0 (Continued)

OVERALL EXTENT OF EXPOSURE TO STUDY AGENT
SAFETY POPULATION
PATIENTS EXPOSED TO STUDY AGENT MORE THAN ONCE

Study	Patient ID (Prior ID)	Treatment Date / Time	Actual Dose (ug) P829 Administered	Actual Dose (mCi) Tc 99m Administered
829-30A	30A-02-04	19JUN96 / 13:15	17.5	17.90
	(30A-02-03)	13JUN96 / 09:15	12.0	16.80
829-32	32-05-11	16JUN97 / 15:12	22.2	18.70
	(32-05-10)	29MAY97 / 09:08	25.6	17.10
829-34A	34A-01-23	21JUL97 / 09:10	50.0	19.18
	(34A-01-22)	09JUL97 / 09:35	12.5	17.46

APPENDIX E

Safety Parameters*

Adverse Events

Vital Signs: Temperature, systolic blood pressure, diastolic blood pressure, pulse, and respiration rate.

Hematology: Hematocrit, hemoglobin, red blood cell count, white blood cell count, platelet count, and differential white blood cell count.

Abbreviated Clinical Chemistry Panel: Blood urea nitrogen (BUN), total protein, serum creatinine, total bilirubin, lactic dehydrogenase (LDH), alkaline phosphatase, AST (SGOT), and ALT (SGPT).

Complete Clinical Chemistry Panel: Albumin, globulin, calcium, chloride, phosphorous, potassium, sodium, carbon dioxide, glucose, urea nitrogen, uric acid, bilirubin (direct and total), creatinine, lactate dehydrogenase (LDH), alkaline phosphatase, creatine kinase, serum glutamic-oxaloacetic transaminase (SGOT/AST), serum glutamic-pyruvic transaminase (SGPT/ALT), gamma-glutamyl transpeptidase (GGT), gastrin, thyroxine (T4), and growth hormone.

Urine Chemistry: color/appearance, specific gravity, pH, protein, glucose, hemoglobin, ketones, bilirubin, occult blood, epithelial cells, urinary sediment and casts.

Immune Response: Immunoglobulin (IgG & IgM) profile form serial serum dilutions.

*** Not all safety parameters were monitored in each clinical study.**

APPENDIX F

Clinical Laboratory Cutpoints

Laboratory Test:	Clinically Significant Cutpoint[2]:
Alkaline phosphatase[1]	≥ 3x UL of the reference range
AST[1]	≥ 3x UL of the reference range
ALT[1]	≥ 3x UL of the reference range
LDH[1]	≥ 3x UL of the reference range
Total protein	≤ 4.5 g/dL
Total bilirubin[1]	≥ 2 mg/dL
BUN[1]	≥ 30 mg/dL
Creatinine[1]	≥ 2 mg/dL
Hematocrit[1]	Male, ≤ 37%; Female, ≤ 32%
Hemoglobin[1]	Male, ≤ 11.5 g/dL; Female, ≤ 9.5 g/dL
RBC count	Male, ≤ 4.0 x 10^6/μL; Female, ≤ 3.9 x 10^6/μL
WBC Count[1]	≤ 2.8 x 10^3/μL or ≥ 16.0 x 10^3/μL
Neutrophils	≤ 20% or ≥ 90%
Basophils	≥ 5%
Eosinophils[1]	≥ 10%
Lymphocytes	≤ 10% or ≥ 60%
Monocytes	≥ 20%
Platelet count[1]	≤ 75 x 10^3/μL or ≥ 700 x 10^3/μL

1 From FDA's Division of Neuropharmacology Drug Products
2 To be flagged as clinically significant the value must have also represented a 25% change from baseline.

JUN 2 3 1999

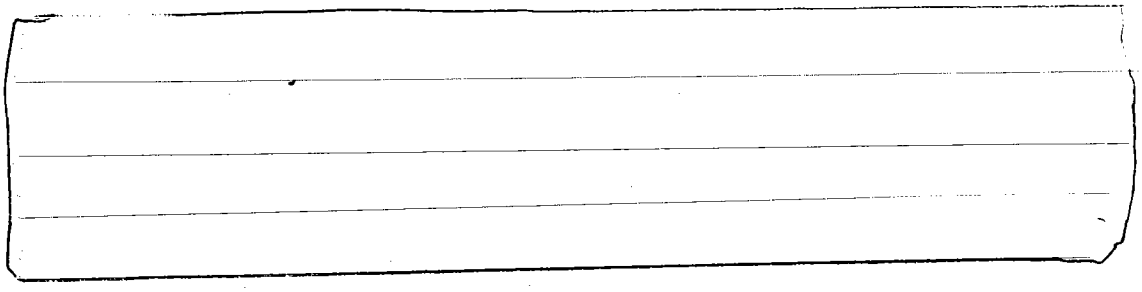
ADDENDUM TO CLINICAL REVIEW OF NDA 21012

NDA 21012
Submission: N000 BL/N000 BZ
Sponsor: Diatide
Drug: NeoTect

Letter Date: 6/8/99, 6/17/99
Stamp Date: 6/10/99, 6/18/99
Completed Date: 7/15/99

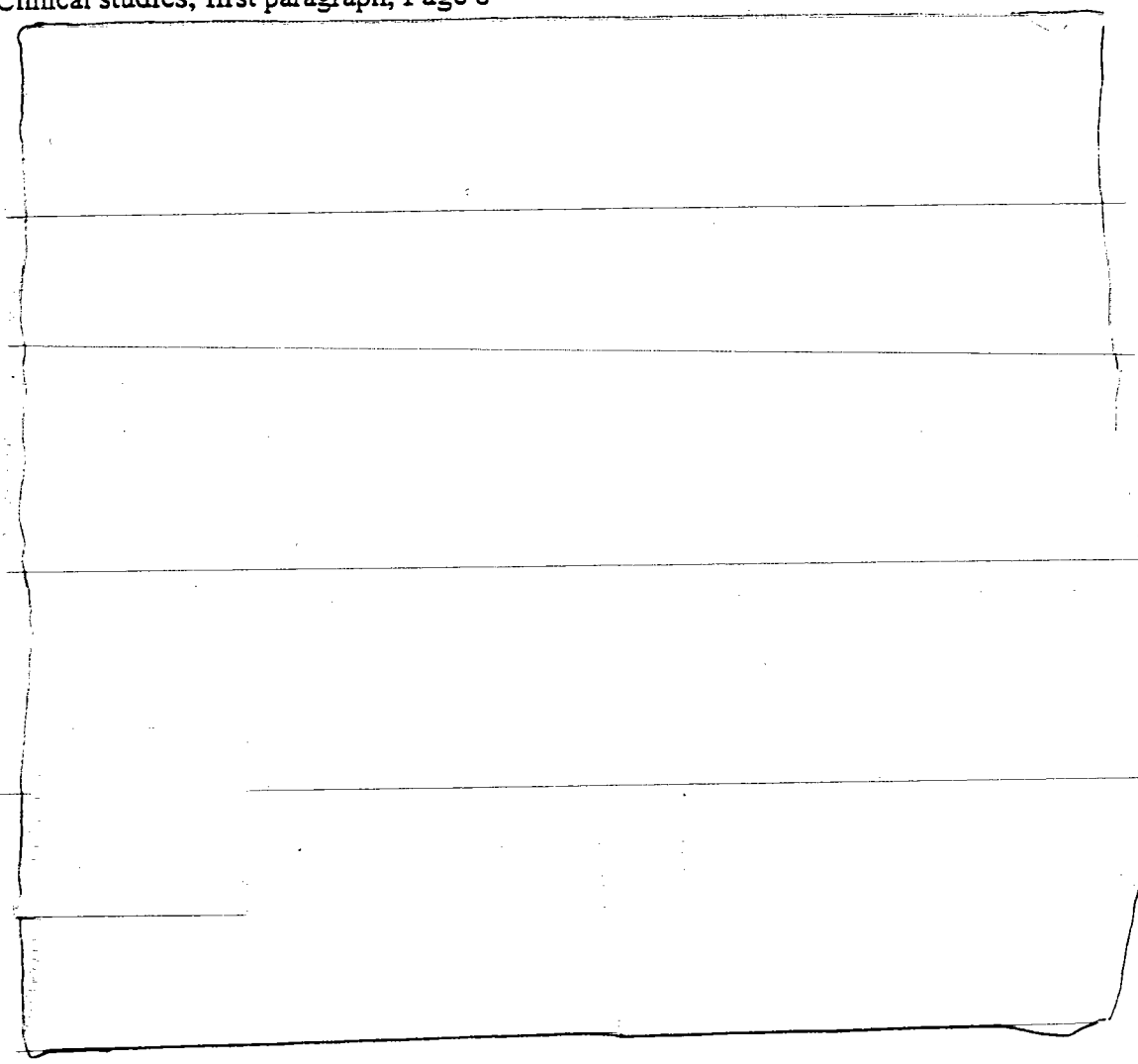
The Sponsor has submitted a revised package insert for NeoTect. The submission includes a list of changes with the Sponsor's rationale for the change followed by a working copy and a clean copy of the insert incorporating the changes. The major Clinical changes that the Sponsor proposes involve the following sections of the package insert: Clinical Studies, Indication and Usage, Adverse Reactions, and Imaging. The Sponsor's changes and rationale (Italics) will be presented followed by reviewer's comments. This reviewer has highlighted any minor word changes within the proposed changed paragraphs for the reader's ease of review

1.) Clinical Studies, first paragraph, Page 7



Reviewer's Comments: (Please see the Attachment 1 of this review for Section 5.2 of the protocol as referenced above by the Sponsor). The primary objective of this study was to compare Neotect images to histopathology using the CT and or chest x-ray as an inclusion criterion. Given that CT and chest x-rays identify anatomical abnormalities and cannot equivocally identify benign versus malignant disease, the comparison of CT to histopathology is less than ideal. Therefore, the comparison of NeoTect to CT, for reasons other than lesion localization, is not appropriate. However, since the CT readers were blinded and were asked to categorize the lesion as either benign or malignant, a comparison was made. Therefore, the Sponsor's change is acceptable. However, it is important to note that specific image criteria for the determination of a malignant versus a benign lesion were not provided.

2.) Clinical studies, first paragraph, Page 8



Rationale *The paragraph as written does not accurately reflect the data. The corrected information better reflects the study results.*

Reviewer's Comment:
The original paragraph is describing the results of a retrospective analysis performed on the pooled pivotal trial data by the Agency's statistician to look for any trends showing an added predictive value of the combined NeoTect and CT results given the independent blinded reader data presented in the NDA. This analysis suggested an additive benefit to the positive predictive value when both CT and NeoTect were positive. Again, this was a retrospective analysis and the results have not been confirmed by a prospective trial.

The data proposed by the Sponsor is the result of a retrospective analysis performed on the pooled pivotal trial data for a subpopulation of patients presenting with a solitary pulmonary nodule (SPN). The results of this blinded read as proposed in the table is misleading and confusing. The mere fact that the NeoTect alone data was not presented in this table offers a slanted picture of the data. If the NeoTect alone data is added to this table (see Table A below), it appears that the combination of NeoTect and CT or chest x-ray improves the sensitivity. However, the combination reads show a decrease in specificity when compared to NeoTect alone. It also suggests that the combination of NeoTect plus chest-x-ray provide better information than that obtained by the CT and NeoTect combination read. This table could lead the reader to believe that CT is not a valuable diagnostic tool when evaluating these patients. It is important to interject here that the concept of combination reads and the benefits of the combination reads were not systematically and prospectively studied in two well-controlled clinical trials. Also, in this retrospective analysis, the Sponsor analyzed a specific subset of SPN patients, those having a non-calcified SPN of 1-3cm. This was performed because this subset is thought to represent the most uncertain diagnostic challenge for the clinician. The results of this data showed lower sensitivities and specificities than reported for SPN of all sizes as seen in the Sponsor's table 8 above. The omission of this data coupled with the data represented in Table 8 is misleading and of questionable use to the clinician. The take home message is that NeoTect should not be used alone and may, when read in combination with CT and or chest x-ray, offer additional clinical information.

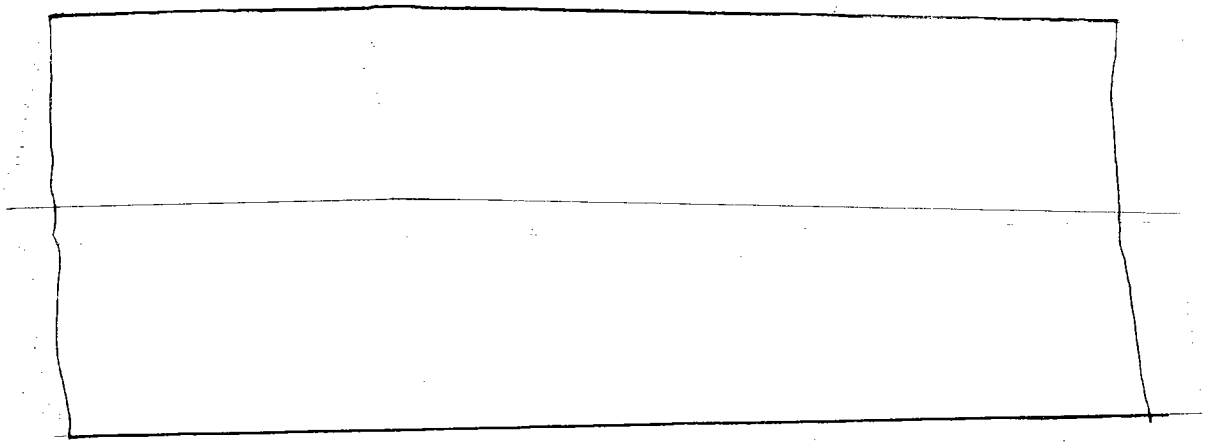
Given that both retrospective analyses have not been confirmed by a prospective trial, it is recommended that the conclusions be briefly stated without citing the specific numerical results.

It is anticipated that the loss in specificity for the combination reads when compared to the NeoTect alone read may be due to the differences in the technology (resolution) of radionuclide scintigraphy compared to CT and chest x-ray, as well as, a lesion tracking problem. This, however, is an assumption by this reviewer and cannot be confirmed or disproved by the data provided.

Table A

	Sensitivity	Specificity	Accuracy
CT Alone	95% [94%, 100%]	7% [0% , 15%]	78% [72% , 84%]
NeoTect Alone	65% [57% , 73%]	85% [74% , 96%]	76% [70% , 82%]
NeoTect plus CT	93% [89% , 97%]	63% [48% , 78%]	87% [82% , 92%]
NeoTect plus Chest X-ray	97% [94% , 100%]	73% [59% , 87%]	91% [87% , 95%]

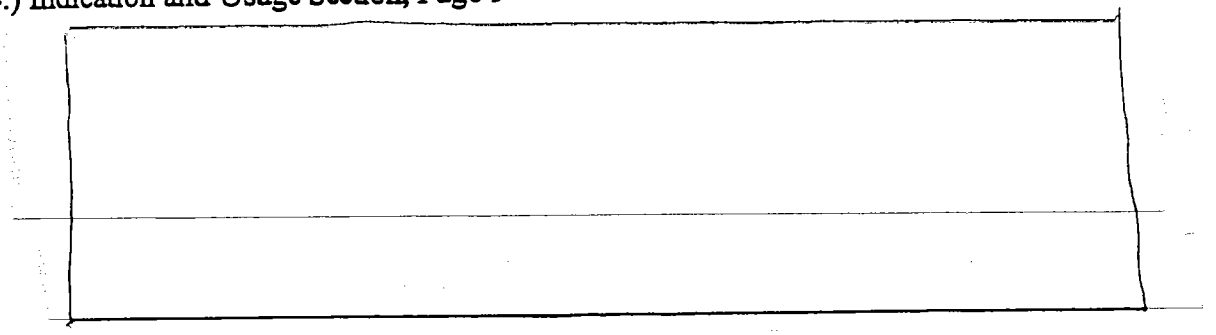
3.) Clinical Studies, fourth paragraph, Page 8



Rationale The pivotal trials were designed to enter patients who presented with a suspicious lesion on chest x-ray and either had or were scheduled to have a CT. The results from the blinded reads in which NeoTect scans were evaluated in the presence of either the chest x-ray or CT image clearly indicate a high level of sensitivity and specificity for NeoTect when used with either chest x-ray or CT.

Reviewer's Comment: Agree to the addition of chest x-ray to this paragraph however it is recommended that **and** be used rather than **or** as the conjunction (e.g. CT **and** chest x-ray).

4.) Indication and Usage Section, Page 9

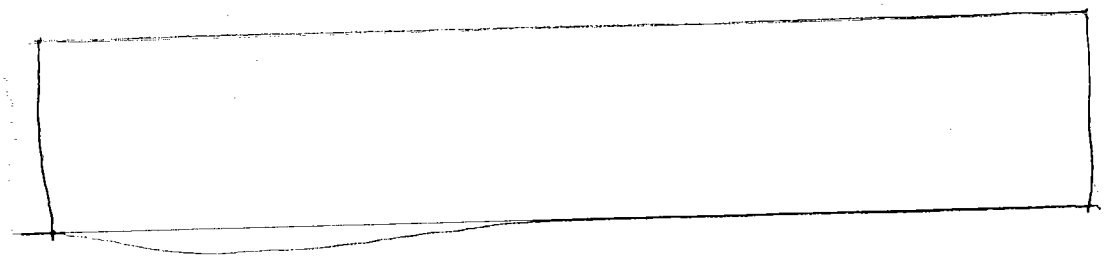


Rationale The pivotal trial design assessed the ability of NeoTect to correctly identify malignant tumors in patients suspicious for lung cancer. The truth standard to which the NeoTect scintigrams were compared was histopathology. Although the mechanism of action of the drug is based on binding to somatostatin receptors, this binding capability was not evaluated in the pivotal trials. The revised indication more accurately reflects the results of the clinical trials conducted to date. The clinical utility for this product is to identify malignant pulmonary masses.

The pivotal trials were designed to enter patients who presented with a suspicious lesion on chest x-ray and either had or were scheduled to have a CT. The results from the blinded reads in which NeoTect scans were evaluated in the presence of either the chest x-ray or CT image clearly indicate a high level of sensitivity and specificity for NeoTect when used with either chest x-ray or CT.

Reviewer's Comments: Since both false positive and false negative results were seen with NeoTect, it is inappropriate to distinguish NeoTect as a drug, which identifies malignant pulmonary masses. Given the specific mechanism of uptake of NeoTect, binding to somatostatin receptors, and the known fact that both benign and malignant tissues have these receptors on their surface, it is more appropriate to label this drug as identifying those pulmonary masses that bear somatostatin receptors.

5.) Adverse Reactions, paragraph 3 to the end, Page 11



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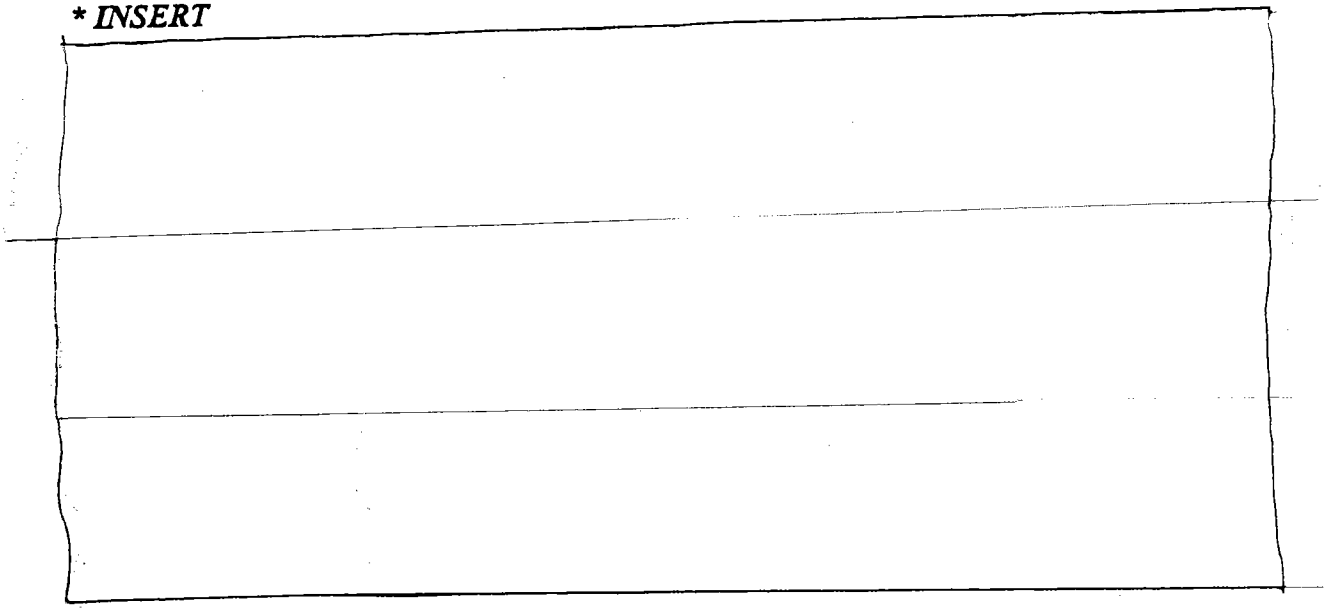

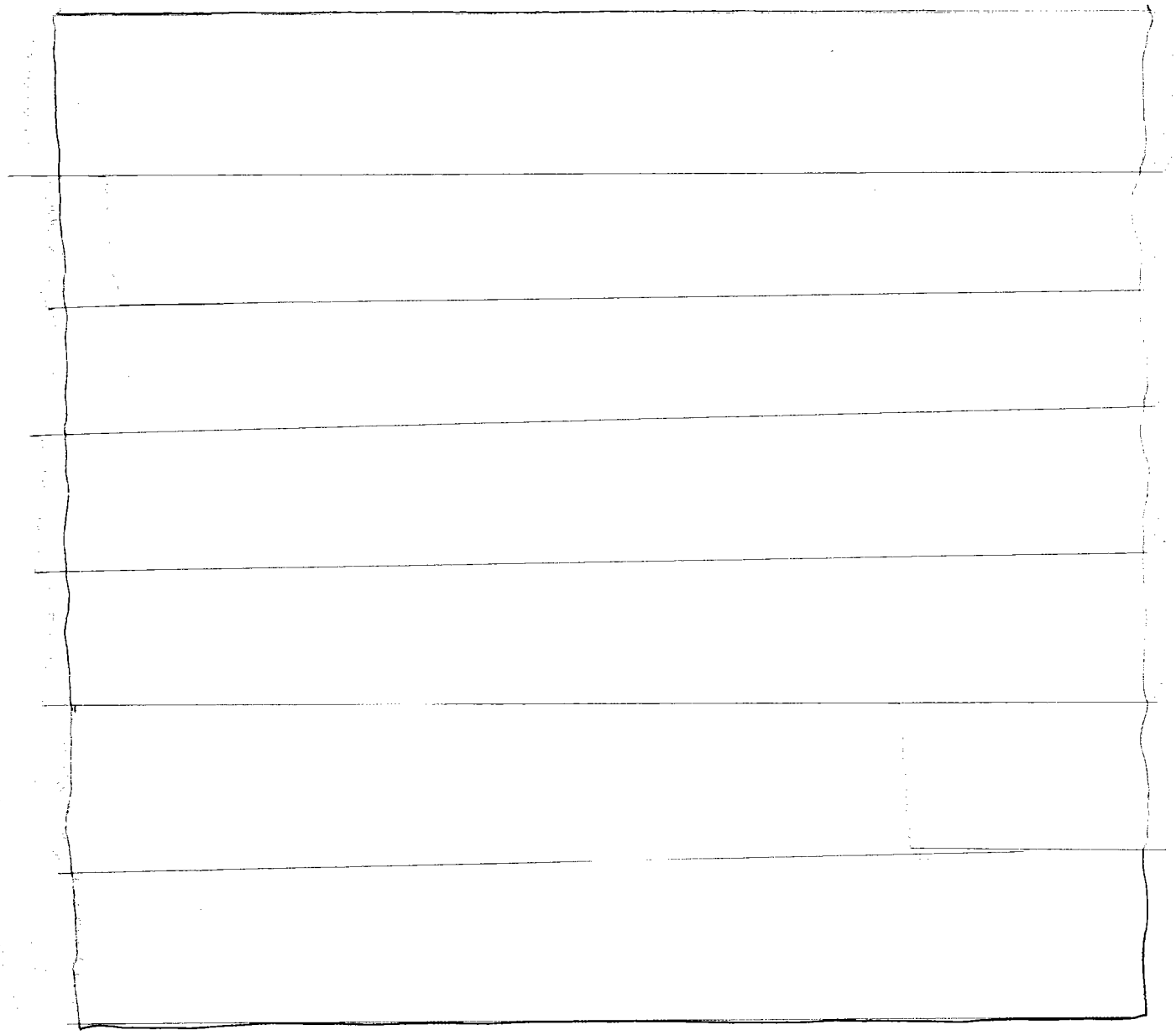

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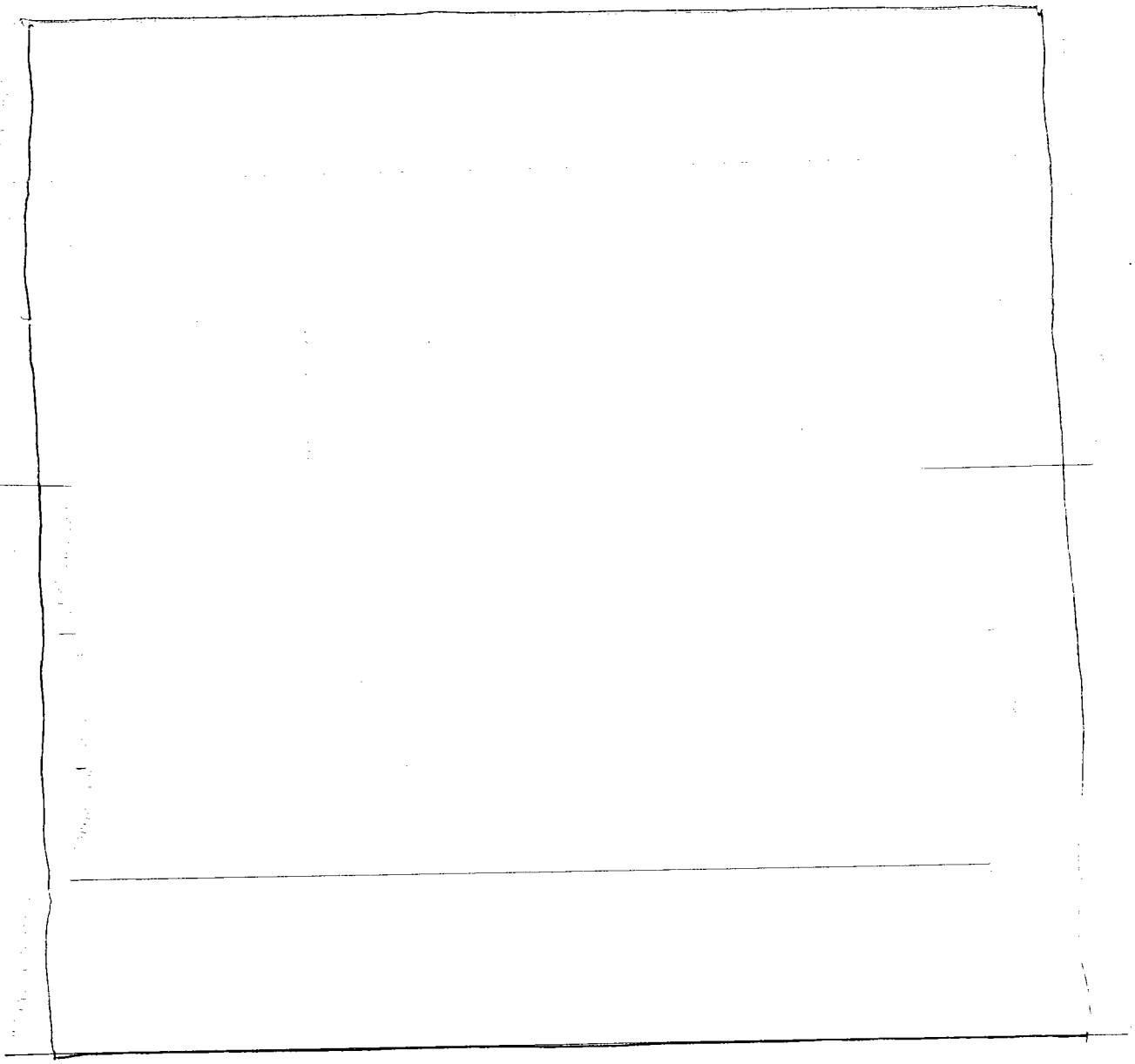
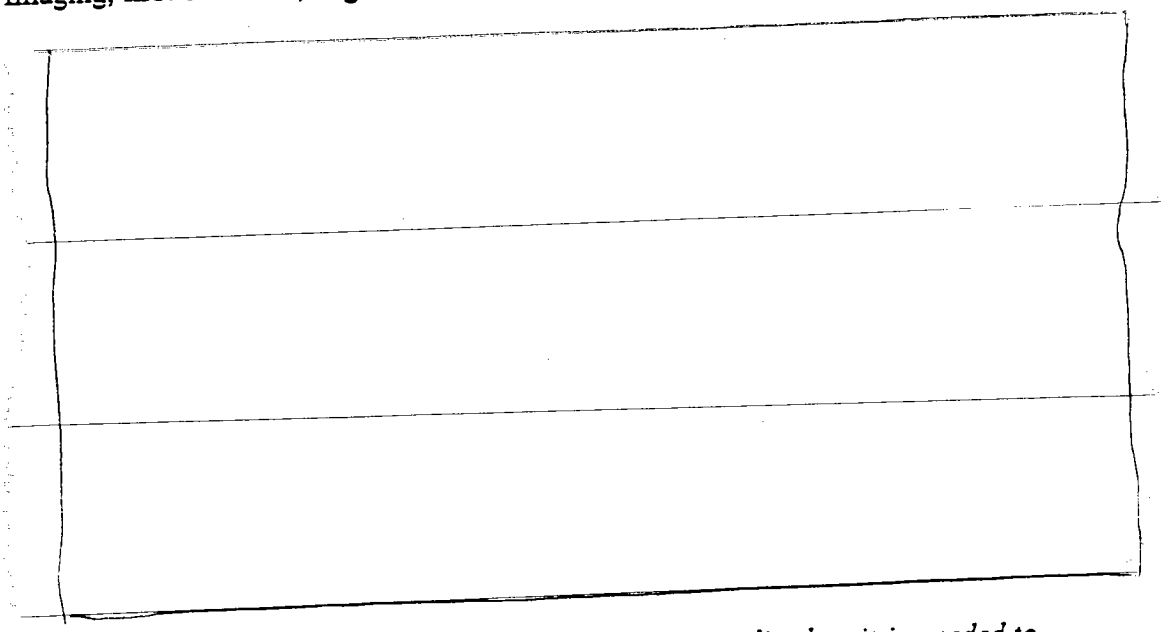
Reviewer's Comments: The data presented should reflect the data collected from patients receiving the market formulation. The Sponsors proposed text for the Adverse Reactions Section does not take this into account. Also, there is an error in the number of serious adverse events reported. The Sponsor identifies 4 serious adverse events in the label, however, the ISS states in the original NDA submission, that there were no serious adverse events reported. The Sponsor was contacted (Facsimile dated 6/11/99) about this discrepancy and has confirmed that there were no serious adverse events reported in any study within NDA 21012 and that the information presented in the label was incorrect (Response submitted 6/17/99, N000 BZ). The method of adverse event reporting within the Sponsor's table 9 is unclear. It appears that the Sponsor has presented adverse events by occurrence in more that one patient. It is proposed that the summary adverse event table list those adverse events as reported in 0.5% or more of the population studied. This reviewer proposes the following for the adverse reaction section of the label.

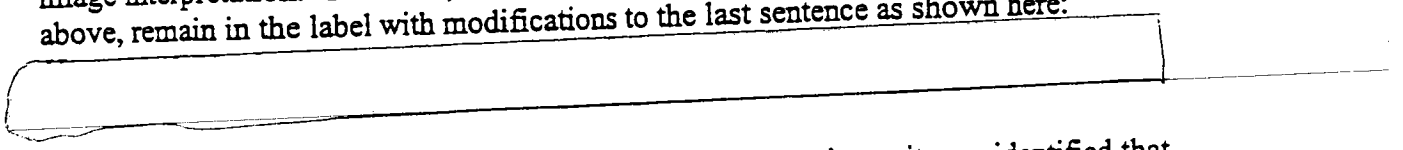


6.) Imaging, first sentence, Page 14

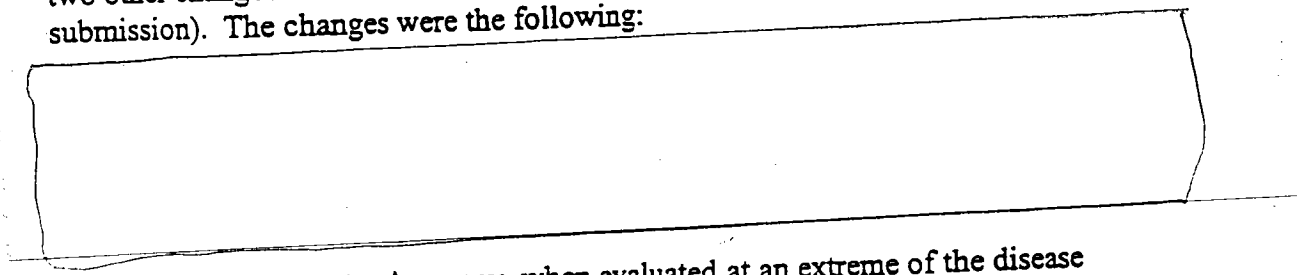


Rationale *It is important that SPECT imaging be utilized as it is needed to properly interpret the NeoTect images. The wording has been changed to strengthen this requirement.*

Reviewer's Comments: In the original response to the approvable letter, the Sponsor stated that both planar and SPECT images of the chest were used for image interpretation. Therefore, the label should reflect this statement. The paragraph proposed by the Sponsor does not clearly state that that the planar image of the chest is required for image interpretation. Therefore, it is recommended that the original paragraph, as shown above, remain in the label with modifications to the last sentence as shown here:



Note: During the review of the working copy of the package insert it was identified that two other changes were made to the clinical studies section of the label (page 13 of the submission). The changes were the following:



Reviewer's Comments: Accuracy, when evaluated at an extreme of the disease continuum, is a distorted test value. In this case the population studied had a high prevalence of disease. This value does not give a true picture of this drug when used in a population other than that studied in the NDA. It has already been stated that this drug cannot be used as a screening tool and would only have potential utility in this limited population.

Therefore, since prevalence of disease is reported along with the sensitivity and specificity of NeoTect, it is not expected that the accuracy values would mislead the clinician.

B.) In the 5th paragraph of the clinical studies section, the Sponsor has added the phrase [redacted]

Reviewer's Comment: This phrase is not necessary since the description of the study design in paragraph clearly states that the image read was blinded.

Reviewer's Conclusions: This reviewer does not agree with the Sponsor's changes labeled above as 2, 4, 5, 6 and B for the reasons stated. The Sponsor's changes labeled as 1, 3 and A are acceptable with some modification. This reviewer proposes an adverse reaction section for the label as shown on page 6 of this review.

/S/

Sally A. Loewke, M.D. 7/21/99
Medical Reviewer

I have discussed the issues in Dr Loewke's review and suggested minor revisions. ~~Her~~ I agree with her comments.

/S/ 7/23/99

A. E. Jones, M.D.
Clinical Team Leader

Generally, I agree with Dr. Loewke's recommendation. However, the wording on the [illegible] needs further revision. For details, see my review of 7/22/99

/S/ 7/23/99

Patricia Y. Love, M.D.
Division Director, HFD-160

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HFD-160 Div. File
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