

Reviewer's Comments: Disagree. No valid conclusions concerning safety can be drawn from this study. This was not a GLP study, and there were numerous inconsistencies that make the results unreliable. For example, the high dose animals came from the supplier in a different shipment, were a different age, and from a different location than the other rats used in this study. Animals for blood collection and necropsy were not randomly selected, instead controls were sampled and sacrificed in the morning and high-dose animals in the afternoon. Also, histopathology was not conducted.

However, to err on the side of safety, one must consider the positive findings in the high-dose group (400 µg peptide/kg/day) as treatment related. Thus, decreased glucose levels in males and females, decreased albumin, albumin/globulin ratio, cholesterol, calcium and phosphorus levels in females, with increased globulin levels are considered treatment-related. Liver weights (absolute and relative) of the females and the relative liver weights of the males were significantly decreased when compared to the control group.

R4.53 A Fourteen-Day Repeated Dose Toxicity Study Of P829 In Sprague-Dawley Rats. Study No. 67089-GLP-94-012.

September 7-21, 1994. Report Dated December 16, 1994. Lot Number 94225-001 (Early Formulation). In Compliance With GLP. Report in Volume 1.13, pp1-130.

Design: This study was designed to assess the toxicity of the original formulation of Tc 99m P829 compared to saline control, after repeated intravenous administration for 14 days in Charles River Sprague-Dawley rats. Three groups of male and female rats (10/sex/group) received repeated injections via the tail vein at dose levels of 0, 30 or 100 µg/kg/day and 2.0 mL/kg. Animals were observed for signs of toxicity immediately, and at 1, 2 and 4 hours after each dose. All rats were sacrificed and day 15, just 24 hours following the last dose on study day 14. Parameters included clinical signs, body weight, hematology (RBC, HGB, HCT, platelets, reticulocytes, WBC and differential), clinical chemistry (Na, K, Cl, Ca, P, CK, AST, ALT, AP, LDH, BUN, glucose, cholesterol, total protein, albumin and globulin), organ weights (liver and spleen), gross and histopathology (15 tissues, control and high-dose group only).

Results: All animals survived to scheduled termination. No treatment-related clinical signs were observed, except some trauma at the injection site which was seen in all groups. There were no significant differences in body weights or body-weight changes between groups, and no group differences in hematology or clinical chemistry were noted. Gross observations at necropsy were sporadic, and no differences existed between groups in terminal body weights or organ weights. Histopathological evaluation did not show a treatment-related response. Hemorrhage, inflammation and hyperkeratosis at the injection site was observed in animals of all groups.

Sponsor's Conclusions: Under the conditions of this study, the repeated-dose intravenous NOEL of Tc 99m P829 (early formulation) was determined to be 100 µg peptide/kg/day administered for 14 days for both male and female Sprague-Dawley rats.

Reviewer's Comments: Agree. There were no treatment-related effects seen in this study in male and female Sprague-Dawley rats, even at the highest dose of 100 µg peptide/kg/day.

R4.54 A Two-Week Toxicity Study Of P829 Administered By Intravenous Injection To Rats. Study No. A817-911.

June 5-20, 1997. Report Dated December 2, 1997. Lot Number 9609B06 (Final Formulation). In Compliance With GLP. Report in Volume 1.13, pp131-320.

Design: This study was designed to assess the toxicity of Tc 99m P829 Injection (final formulation) compared to saline control, when administered to Charles River Sprague-Dawley, CrI:CD® rats for 14 consecutive days. The test material was supplied by the Sponsor to the test facility in 2 separate components; 1) Kit for preparation of Technetium Tc-99m P829, and 2) Decayed Tc-99m generator eluate. Just prior to dosing, the kits were reconstituted with saline and decayed generator eluate to yield concentrations equal to the recommended human dose. After reconstitution, the vials were heated in a boiling water bath for 10 minutes, then allowed to cool at room temperature for 15 minutes prior to dosing. Three groups of male and female rats (10/sex/group) received repeated daily injections via the tail vein at dose levels of 0, 40 or 100 µg peptide/kg/day and a volume of 2.0 ml/kg. Animals were observed for signs of toxicity immediately after each dose and at 1, 2 and 4 hours. Rats were sacrificed on day 15, just 24 hours following the last dose on study day 14. Parameters included clinical signs, body weight, hematology (RBC, HGB, HCT, platelets, reticulocytes, WBC and differential), clinical chemistry (Na, K, Cl, Ca, P, CPK, GGT, AST, ALT, AP, LDH, BUN, glucose, cholesterol, triglycerides, total protein, albumin and globulin), organ weights (adrenal, brain, liver and spleen), gross and histopathology (44 tissues, control and high-dose group only).

Results: All animals survived to scheduled termination, except for one control female that died of asphyxiation during restraint for dosing. No clinical signs or effects on body weight were observed. Statistically significant increases in alkaline phosphatase (males and females), and albumin (males) were observed in the high-dose group. No differences were noted for hematology or other clinical chemistry parameters. No differences in body weight or body-weight changes were noted. Gross necropsy findings were sporadic and not considered treatment-related, as were inconsistent variations in organ weight values. Histopathological evaluation of the tissues from the control and high-dose groups did not show treatment-related effects.

Sponsor's Conclusions: Administration of Tc 99m P829 Injection at dose levels of 40 and 100 µg peptide/kg/day for 14 consecutive days was not attributed to any adverse effect. Under the conditions of this study, repeated-dose intravenous NOEL of Tc 99m P829 Injection was determined to be 100 µg peptide/kg/day administered for 14 days for both male and female Sprague-Dawley rats.

Reviewer's Comment: Agree. There were no treatment-related effects observed in rats receiving Tc 99m P829 Injection for 14 days at 40 and 100 µg peptide/kg/day.

R4.55. A Ten Day Repeated Dose Toxicity Study Of P829 In New Zealand White Rabbits. Study No. 67083.

August 15-25, 1994. Report Dated October 24, 1994. Lot Number 940013 (Early Formulation). Not In Compliance With GLP. Report In Volume 1.13, pp 321-411.

Design: This study was designed to assess the toxicity of unformulated Tc 99m P829 compared to saline controls for 10 days in New Zealand White rabbits. The P829 trifluoroacetate was reconstituted with Glucoscan[®] and saline and not heated. Glucoscan[®] is manufactured by Dupont Merck and is the kit for preparation of technetium Tc 99m Gluceptate and contains 200 mg Gluceptate sodium and 0.06 mg stannous chloride. The rabbits were supplied by [redacted] and weighed 2.3-2.5 kg and were 11-12 weeks of age. Three groups of male and female rabbits (6/sex/group) received repeated injections via the marginal ear vein at dose levels of 0, 100 or 400 µg peptide/kg/day and a volume of 1.0 ml/kg. Animals were observed for signs of toxicity immediately after each dose, and at 1, 2 and 4 hours. Rabbits were sacrificed on day 11, just 24 hours after the last dose on study day 10. Parameters included clinical signs, body weight, hematology (RBC, HGB, HCT, platelets, reticulocytes, WBC and differential), clinical chemistry (Na, K, Cl, Ca, P, CPK, GGT, AST, ALT, AP, LDH, BUN, glucose, cholesterol, triglycerides, total protein, albumin and globulin), organ weights (liver and spleen), gross and histopathology (only on gross lesions from just a few animals).

Results: All animals survived to scheduled termination. No treatment-related clinical signs were noted during the study. The females exhibited a significantly lower terminal body weight and reduced body weight gain compared to control animals. The values for males were also lower, but not significantly. There was a significant decrease in mean monocyte count in the high dose females, with no other hematology parameters that differed significantly from the control group. Calcium, total protein, albumin and albumin/globulin ratios were significantly decreased for high-dose males and females compared to the controls. No other clinical chemistry parameters were significantly different from control values. Absolute liver weights were reduced in the high-dose males and females when compared to the controls. Sporadic gross findings included red foci of the cervical lymph nodes, lungs, and pituitary (high-dose female). These gross findings were related to agonal changes of the pituitary, pulmonary inflammation and congestion with lymphoid hyperplasia, similar in both control and Tc 99m P829-treated rabbits.

Sponsor's Conclusions: Based on the results of this study, the repeated-dose intravenous NOEL of Tc 99m P829 as P829 peptide trifluoroacetate reconstituted with Glucoscan[®] is 100 µg peptide/kg/day administered for 10 days for male New Zealand white rabbits and less than 100 µg peptide/kg/day for female rabbits.

Reviewer's Comments: Disagree. Tc 99m P829-related effects observed in the 400 µg peptide/kg/day group included decreased body weights and body-weight gains in females and calcium, total protein, albumin and albumin/globulin ratios significantly decreased for males and females. Female rabbits in the 100 µg peptide/kg/day group demonstrated decreases in total protein and albumin. A NOEL was not achieved in this study.

R4.56 A Fourteen Day Repeated Dose Toxicity Study Of P829 In New Zealand White Rabbits. Study No. 67087.

September 8-22, 1994. Report Dated December 16, 1994. Lot Number 94225-001 (Early Formulation). In Compliance With GLP. Report In Volume 1.14, pp 1-125.

Design: This study was designed to assess the toxicity of the original formulation of Tc 99m P829, compared to saline controls, after repeated daily administration to albino New Zealand White rabbits for 14 days. The animals were supplied by [redacted] and were 11-12 weeks of age and weighed 2.2-2.7 kg. Three groups of male and female rabbits (6/sex/group) received repeated injections via the marginal ear vein of Tc 99m P829 at dose levels of 0, 30 or 100 µg peptide/kg/day and volume of 2.0 mL/kg. Animals were observed for signs of toxicity immediately after each dose and at 1, 2 and 4 hours. Rabbits were sacrificed on day 15, just 24 hours after the last dose on study day 14. Parameters included clinical signs, body weight, hematology (RBC, HGB, HCT, platelets, reticulocytes, WBC and differential), clinical chemistry (Na, K, Cl, Ca, P, CK, AST, ALT, AP, LDH, BUN, glucose, cholesterol, total protein, albumin and globulin), organ weights (liver and spleen), gross and histopathology (15 tissues, control and high-dose groups only).

Results: All animals survived to scheduled termination. No changes in clinical signs, body weight or body-weight changes, organ weights, hematology, or clinical chemistry parameters were treatment-related. Gross findings at necropsy were limited to effects associated with intravenous injection seen in all groups, with no histopathological effects that were considered treatment related.

Sponsor's Conclusions: Under the conditions of this study, the repeated-dose intravenous NOEL of Tc 99m P829 (early formulation) was determined to be 100 µg peptide/kg/day administered for 14 days for both male and female New Zealand white rabbits.

Reviewer's Comments: Agree. No treatment-related effects were seen when New Zealand White rabbits received either 30 or 100 µg peptide/kg/day of an early formulation of Tc 99m P829 for 14 days.

R4.57 A Two-Week Toxicity Study Of P829 Administered By Intravenous Injection To Rabbits. Study No. A818-911. [redacted] May 29- June 13, 1997. Report Dated December 3, 1997. Lot Number 9609B06 (Final Formulation). In Compliance With GLP. Report In Volume 1.14, pp 126-239.

Design: This study was designed to assess the toxicity of Tc 99m P829 Injection (final formulation), compared to saline control, when administered to albino rabbits for 14 consecutive days. The animals were supplied by [redacted] and identified as Albino SPF-NZW®, [Hra:(NZW)SPF], weighing 1.8-2.7 kg and 12-14 weeks of age. The test material was supplied by the Sponsor to the test facility in 2 separate components; 1) Kit for preparation of Technetium Tc-99m P829, and 2) Decayed Tc-99m generator eluate. Just prior to dosing each day, the kits were reconstituted with decayed generator eluate and saline to yield concentrations equal to the recommended human dose. After reconstitution, the vials were heated in a boiling water bath for 10 minutes, then allowed to cool at room temperature for 15 minutes prior to dosing. The final dosing solution concentration was 50 µg peptide/mL. The dosing solutions were prepared fresh each day and dosed within 6 hours. Three groups of male and female rabbits (6/sex/group) received daily injections via the marginal ear vein at dose levels of 0, 40 or 100 µg peptide/kg/day and 2.0 ml/kg/day. Animals were observed for signs of toxicity immediately after each dose, and at 1, 2 and 4 hours. Rabbits were sacrificed on day 15, just 24 hours following the last dose on study day 14. Parameters included clinical signs, body weight, hematology (RBC, HGB, HCT, platelets, reticulocytes, WBC and differential), clinical chemistry (Na, K, Cl, Ca, P, CK, AST, ALT, AP, LDH, BUN, glucose, cholesterol, total protein, albumin and globulin), organ weights (adrenal, brain, liver and spleen), gross and histopathology (45 tissues, control and high-dose group only).

Results: All animals survived to scheduled termination. No effects on clinical signs or body weights were observed, with no treatment-related differences seen in any of the clinical chemistry parameters. Inconsistent variations in BUN, triglycerides and RBC are not considered treatment related. Sporadic gross findings at necropsy were limited to liver, thymus, adrenal, ovary, epididymus and testes and are not considered related to treatment. Histopathology of tissues from control and high-dose animals did not show effects that are related to treatment. There was a statistically significant decrease in the absolute liver weights and ratio of liver:body weight in the high-dose females. There were no correlative histopathological or chemistry changes. However, as seen in the table below, changes appear to be treatment related, with the trend of decreased absolute liver weight and ratios being consistent from control to high-dose group for both males and females.

Table: Mean Body Weights, Liver Weights and Liver-to-Body Weight Ratios (Mean \pm SD)

Group	Sex/n	Terminal Body Wt(kg)	Liver Wt. (g)	Ratio (Liver/Body Wt $\times 10^2$)
Control (Saline)	M/6	2.8 \pm 0.1	77.2 \pm 3.4	2.73 \pm 0.18
Control (Saline)	F/6	2.6 \pm 0.2	70.3 \pm 4.1	2.71 \pm 0.11
40 μ g/kg/day	M/6	2.8 \pm 0.1	75.1 \pm 4.9	2.67 \pm 0.17
40 μ g/kg/day	F/6	2.6 \pm 0.1	67.6 \pm 5.7	2.62 \pm 0.27
100 μ g/kg/day	M/6	2.8 \pm 0.1	71.6 \pm 6.6	2.53 \pm 0.73
100 μ g/kg/day	F/6	2.6 \pm 0.1	60.3 \pm 6.5 *	2.33 \pm 0.96 *

* Significantly decreased $p < 0.05$.

Sponsor's Conclusions: Administration of Tc 99m P829 Injection at dose levels of 40 and 100 μ g peptide/kg/day for 14 consecutive days was not associated with any adverse effect. Under the conditions of this study, the repeated-dose intravenous NOEL of Tc 99m P829 Injection was determined to be 100 μ g peptide/kg/day administered for 14 days for both male and female New Zealand white rabbits.

Reviewer's Comment: Disagree. The reduction of liver weight and liver-to-body weight ratio in the high-dose females is considered a treatment-related effect. There was also a reduction for the males, but it was not a statistically significant decrease. For the males and females in this study, mean values for liver weight and liver/body weight ratios decreased consistently from control to mid dose to high dose, respectively. Thus, for this study the NOEL is 40 μ g peptide/kg/day of Tc 99m P829 Injection (final formulation) for the New Zealand White rabbit after 14 days of administration.

30. CARCINOGENICITY STUDIES: None conducted.

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31. IMMUNOTOX STUDIES:**R4.59 Systemic Antigenicity Study In The Guinea Pig. Study No. 96T-13730-00.**

October 9-November 18, 1996. Report Dated April 10, 1997. Lot Number 9609B01 (Final Formulation). In Compliance With GLP. Report In Volume 1.14, pp 256-275.

Design: This study was designed to assess the antigenic potential of Tc 99m P829 Injection in guinea pigs when administered for a 2-week sensitization period, followed by an intravenous challenge. Test animals were supplied by Charles River and designated as young adult Crl:(HA)BR albino guinea pigs and weighing 311-371 g. One group of 6 male guinea pigs received 6 ml intraperitoneal injections containing 50 µg peptide, 3 times a week for 2 weeks for a total of 6 injections. Fifteen and 29 days after the final sensitization injection, 3 guinea pigs per time point, received a 2 ml challenge injection of Tc 99m P829 Injection via the ear vein. Control animals received saline. Animals were observed for signs of anaphylactic response for 15 minutes immediately following the challenge dose.

Results: All animals survived to scheduled termination. No signs of anaphylactic response were observed following the intravenous challenge in any guinea pigs receiving Tc 99m P829 Injection or the saline control.

Sponsor's Conclusion: Under the conditions of this study, Tc 99m P829 Injection is considered non-antigenic in the guinea pig.

Reviewer's Comment: Agree. There was no indication of anaphylactic responses in this study. It is therefore concluded that Tc 99m P829 Injection is not a systemic antigen in the guinea pig.

32. REPRODUCTIVE TOXICOLOGY STUDIES: None conducted. Diatide Inc. has requested a waiver in accordance with 21 CFR ¶ 314.90.

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33. GENOTOXICITY STUDIES

R4.63 Mutagenicity Test With Peptide P829 In The Salmonella - Escherichia coli/Mammalian-Microsome Reverse Mutation Assay Preincubation Method With A Confirmatory Assay. Study No. 17618-0-422R.

Study Dates, April 30-May 17, 1996. Report Dated September 5, 1996. Lot Number YWC-005-155 (Peptide P829). In Compliance With GLP. Report In Volume 1.14, pp 299-330.

Design: This study was designed to assess the ability of the peptide P829, to induce reverse mutations either in the presence or absence of mammalian microsomal enzymes at either the histidine locus in the genome of Salmonella typhimurium or the tryptophan locus of Escherichia coli strain WP2uvrA. The cytotoxicity of peptide P829 was determined at the dose levels of 0.512, 1.54, 5.12, 15.4, 51.2, 154, and 386 µg peptide/ml, in order to select the appropriate doses for the mutagenicity assay. The mutagenicity assay was performed using tester strains TA98, TA100, TA1535, TA1537 and WP2uvrA. The tester strains were exposed to peptide P829, in the presence and absence of Aroclor-induced rat hepatic S9 preparation. The dose levels selected, based on the results of the dose range-finding study, were 5.12, 15.4, 51.2, 154 and 385 µg peptide/ml of preincubation reaction mixture for the initial mutation assay. After a review of the assay results, a confirmatory assay was conducted with test article concentrations of 1.54, 5.12, 15.4, 51.2, 154 and 385 µg peptide/ml of preincubation reaction mixture, except the TA100 strain which tested at 0.512, 1.54, 5.12, 15.4, 51.2, and 154 µg peptide/ml of preincubation reaction mixture. Prior to evaluation of the assay, the criteria for a valid assay were defined, and included tester strain integrity, tester strain culture density, positive control values and cytotoxicity. Criteria for a positive response in the plate incorporation assay was defined as a 2-fold (TA98, TA100, WP2uvrA) or 3-fold (TA1535 and TA1537) increase in the mean revertants per plate of at least one of the tester strains over the mean revertants per plate of the vehicle control. The increase in the mean number of revertants required an accompanying dose response to increasing concentrations of peptide P829.

Results: In the initial mutagenicity assay and in the confirmatory assay, no positive increases were observed with any of the tester strains with or without metabolic activation with Aroclor-induced S9 liver homogenate. Adequate cytotoxicity was achieved to consider this a valid assay, with the two highest concentrations exhibiting >80% cytotoxicity. Responses of vehicle controls and positive controls (2-aminoanthracene, 2-nitrofluorene, sodium azide, ICR-191, and 4-nitroquinoline-N-oxide) were as expected.

Sponsor's Conclusions: The results indicate that Peptide P829 is non-mutagenic in the Salmonella - Escherichia coli/mammalian-microsome reverse mutation assay at the maximum dose of 385 µg peptide/ml of preincubation mixture.

Reviewer's Comment: Agree. There is no evidence of mutagenic activity by peptide P829 in this assay.

R4.64 Mutagenicity Test With Kit For The Preparation Of Technetium Tc 99m In The Salmonella - Escherichia coli/Mammalian-Microsome Reverse Mutation Assay Preincubation Method With A Confirmatory Assay. Study No. 18037-0-422R. Study Dates, November 15-December 16, 1996. Report Dated August 1, 1997. Lot Number 9609B01 (Final Formulation). In Compliance With GLP. Report In Volume 1.14, pp 332-368.

Design: This study was designed to assess the ability of the Kit for Preparation of Technetium Tc 99m P829 Injection, to induce reverse mutations either in the presence or absence of mammalian microsomal enzymes at either the histidine locus in the genome of Salmonella typhimurium or the tryptophan locus of Escherichia coli strain WP2uvrA. Cytotoxicity was determined at the dose levels of 0.000162, 0.00192, 0.00612, 0.0192, 0.0612, 0.192, 0.612, 1.92, 6.2 and 19.2 µg peptide/ml, in order to select the appropriate doses for the mutagenicity assay. The mutagenicity assay was performed using tester strains TA98, TA100, TA1535, TA1537 and WP2uvrA. The tester strains were exposed to the test article in the presence and absence of Aroclor-induced rat hepatic S9 preparation. The dose levels, selected based on the results of the dose rangefinding study, were 0.192, 0.612, 1.92, 6.12 and 19.2 µg peptide/ml of preincubation reaction mixture for the initial mutation assay. After review of the first assay results, a confirmatory assay was conducted with the same test article concentrations of 0.192, 0.612, 1.92, 6.12 and 19.2 µg peptide/ml of preincubation reaction mixture. Prior to evaluation of the assay, the criteria for a valid assay were defined, and included tester strain integrity, tester strain culture density, positive control values and cytotoxicity. Criteria for a positive response in the plate incorporation assay was defined as a 2-fold (TA98, TA100, WP2uvrA) or 3-fold (TA1535 and TA1537) increase in the mean revertants per plate of at least one of the tester strains over the mean revertants per plate of the vehicle control. The increase in the mean number of revertants required an accompanying dose response to increasing concentrations of Tc 99m P829 Injection.

Results: In the initial mutagenicity assay and in the confirmatory assay, no positive increases were observed with any of the tester strains with or without metabolic activation with Aroclor-induced S9 liver homogenate. Adequate cytotoxicity was achieved to consider this a valid assay, with the two highest concentrations exhibiting >80% cytotoxicity. Responses of vehicle controls and positive controls (2-aminoanthracene, 2-nitrofluorene, sodium azide, [redacted] 191, and 4-nitroquinoline-N-oxide) were as expected.

Sponsor's Conclusions: The results indicate that Tc 99m P829 Injection is non-mutagenic in the Salmonella - Escherichia coli/mammalian-microsome reverse mutation assay at the maximum dose of 19.2 µg peptide/ml of preincubation mixture.

Reviewer's Comments: Agree. There is no evidence of mutagenic activity by the Kit for the Preparation of Technetium Tc 99m in this assay.

R4.66 Mutagenicity Test With Kit For The Preparation Of Technetium Tc 99m In An *in vivo* Mouse Micronucleus Assay. Study No. 18037-0-455CO. [REDACTED]

[REDACTED] Study Dates, November 12, 1996-June 20, 1997. Report Dated October 21, 1997. Lot Number 9609B01 (Final Formulation). In Compliance With GLP. Report In Volume 1.15, pp 36-66.

Design: This study was designed to assess the ability of the Kit For The Preparation of Technetium Tc 99m P829 to induce clastogenic effects or disruption of the mitotic apparatus by detecting micronuclei in polychromatic erythrocyte stem cells in Charles River, Crl:CD-1 [REDACTED] BR mouse bone marrow. Ten animals per sex were assigned to each dose group. In the first of two micronucleus studies, Kit for the Preparation of Technetium Tc 99m P829 was reconstituted in decayed Technetium Tc 99m generator eluate, heated and dosed by intravenous injection at dose levels of 0, 1.0, 2.0 and 4.0 mg peptide/kg. The mice were euthanized 24, 48, and 72 hours after dosing for extraction of the bone marrow in the first study. In the second micronucleus study the Kit for the Preparation of Technetium Tc 99m P829 was reconstituted in synthetic Technetium Tc 99m decayed generator eluate, heated and dosed by intravenous injection at dose levels of 0, 2.0 and 4.0 mg peptide/kg. The mice were euthanized 24 and 48 hours after dosing for extraction of the bone marrow in the second study. In both studies, cyclophosphamide at a dose of 80 mg/kg served as the positive control with these animals being euthanized 24 hours after treatment. The criteria for a positive response consisted of a statistically significant dose-related increase in micronucleated polychromatic erythrocytes and a statistically significant positive response for at least one dose level.

Results: All animals survived to scheduled termination. All vehicle and positive control animals appeared normal immediately after dosing and throughout the study observation period. Clinical signs in Tc 99m P829 Injection-treated animals included hypoactivity, hunched appearance, squinted eyes and prostration, which cleared within an hour after dosing. Technetium Tc 99m P829 Injection did not induce increases in micronucleated polychromatic erythrocytes over the levels observed in the vehicle controls in either sex or at any of the harvest times in either study. The positive control, cyclophosphamide, induced significant increases in micronucleated polychromatic erythrocytes in both males and females in both studies. Incidence values ranged from 4.9-5.9% in males and 2.3-2.8% in females.

Sponsor's Conclusions: The results indicate that Tc 99m P829 Injection did not induce significant signs of toxicity nor an increase in micronuclei in bone marrow PCE in either study and therefore is considered negative.

Reviewer's Comments: Agree. The Kit For Preparation of Technetium Tc 99m P829 Injection did not induce significant increases in micronuclei in bone marrow polychromatic erythrocytes in either the first or second study and is not considered clastogenic in the mouse bone marrow micronucleus test. However, at dose levels of 1, 2 and 4 mg peptide/kg, clinical signs of toxicity were observed; namely, hypoactivity, hunched posture, squinted eyes and prostration. These effects cleared within an hour after dosing.

R4.65 Mutagenicity Test on "Kit For The Preparation of Technetium Tc 99m Depreotide" (Mock Labeled) in the L5178Y TK⁺ Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay. Study Number 18037-0-431R. [redacted]
[redacted] Study Dates, October 30-December 26, 1996. Report Dated August 21, 1997. Lot Number 9609B01 (Final Formulation). In Compliance With GLP. Report In Volume 1.15, pp 2-34.

Design: This study was designed to assess the ability of the "Kit For The Preparation of Technetium Tc 99 Depreotide" to induce mutations at the thymidine kinase locus in cultured L5178Y cells. The test material was supplied by the Sponsor to the test facility in 2 separate components; 1) Kit for preparation of Technetium Tc-99m P829, and 2) Decayed Tc-99m generator eluate. Just prior to dosing, the kits were reconstituted with decayed generator eluate and saline to yield concentrations equal to the recommended human dose. After reconstitution, the vials were heated in a boiling water bath for 10 minutes, then allowed to cool at room temperature for 15 minutes prior to dosing. "Kit For The Preparation of Technetium Tc 99m Depreotide" remained in solution in culture medium up to 2.5 μg of P829/ml, but higher concentrations were cloudy. Cytotoxicity was first estimated in a prescreen by exposing cells to 10 concentrations ranging from 0.00977 μg of P829/ml to 5 μg of P829/ml, with and without S9 activation from Aroclor 1254 induced male Sprague-Dawley rat liver homogenate. Results of the toxicity prescreen indicated "Kit For The Preparation of Technetium Tc 99m Depreotide" with and without metabolic activation was noncytotoxic at all dose levels. Doses selected for the mutation assays were based on the results from the dose range finding assay, where solubility limited the highest concentrations used.

Results: Two nonactivation mutation assays were conducted with "Kit For The Preparation of Technetium Tc 99m Depreotide" in cultures that were not activated with S9. In both trials, six treatments were evaluated: 0.156, 0.313, 0.625, 1.24, 2.50 and 5.00 μg P829/ml. All six treatments were noncytotoxic, however, insolubility in the two highest concentrations was limiting. In order for a culture to be considered as mutagenic in the first trial, a mutant frequency greater than 77.7×10^{-6} was required. In the second trial, a mutant frequency greater than 190.7

$\times 10^{-6}$ was required. These threshold values were twice the average mutant frequency of the concurrent vehicle control values. None of the assayed treatments in either trial induced this level of mutant action and no dose related trend was observed. Two trials of the activation assay were performed with six dose levels being evaluated in both trials: 0.156, 0.313, 0.625, 1.24, 2.50 and 5.00 μg P829/ml. "Kit For The Preparation of Technetium Tc 99m Depreotide" was not cytotoxic at any of the six doses used. In order for a culture to be considered as mutagenic in the first trial, a mutant frequency greater than 93.4×10^{-6} was required. In the second trial, a mutant frequency greater than 185.9×10^{-6} was required for a positive evaluation. These threshold values were twice the average mutant frequency of the concurrent vehicle control values. None of the assayed treatments in either trial induced this level of mutant action and no dose related trend was observed. Therefore, the minimum criteria required for a positive response was not met. The average cloning efficiencies for the vehicle controls with and without S9 activation demonstrated acceptable cloning conditions for the assays. The positive control cultures for nonactivation mutation studies with methyl methanesulfonate at 5 - 10 nl/ml, induced mutant frequency increases of 6.8 fold above the background mutant frequency. The positive control cultures for S9 activation mutation studies with methylcholanthrene at 2.0 - 4.0 $\mu\text{g}/\text{ml}$, induced mutant frequency increases of 9.2 fold above the background mutant frequency.

Sponsor's Conclusions: The results indicate that Tc 99m P829 Injection is non-mutagenic in the L5178Y TK ⁺ mouse lymphoma forward mutation assay at the maximum dose of 5.0 μg peptide/ml.

Reviewer's Comment: None of the evaluated treatments in any of the trials with and without activation with S9 liver homogenate induced a mutant frequency that exceeded the minimum criterion and no dose-related trend was observed. Tc 99m P829 Injection is therefore considered nonmutagenic in the L5178Y TK ⁺ mouse lymphoma forward mutation assay.

34. Special Toxicology Studies

R4.23 An Evaluation Of The Compatibility Of Technetium Tc 99m P829 Injection Prepared With Decayed Generator Eluate With Human Blood Or Serum. Laboratory, Diatide Inc., Londonderry, NH. Study Date, September 10, 1996. Report Dated February 2, 1998. Lot Number 9609B01(Final Formulation). Not Required To Be In Compliance With GLP. Report in Volume 1.14, pp241-255.

Design: This study was designed to assess in vitro blood compatibility of Technetium Tc 99m P829 Injection prepared with decayed generator eluate. Technetium Tc 99m P829 Injection is administered as a bolus injection where, as a result, the intravascular compartment is exposed to high concentrations of the drug for short periods. The compatibility of Technetium Tc 99m P829 Injection with whole blood or serum at room temperature was tested at dilutions of 1:4 and

1:8 (Tc 99m P829 Injection: blood or serum). Identical dilutions of saline with blood or serum served as control. Two adult volunteers provided 40 ml blood for serum separation and 30 ml whole blood with NaEDTA anticoagulant. The following parameters were evaluated: erythrocyte sedimentation rate (ESR), leukocyte (WBC) count and morphology, erythrocyte (RBC) count, MCV, MCH, MCHC, platelet count, platelet appearance (clumping), Rouleaux formation, plasma protein precipitation and serum protein precipitation.

Results: No notable differences in hematologic parameters, except those from dilution, were found in comparing each subject's normal hematology values with samples to which saline and Technetium Tc 99m P829 Injection had been added. Only one subject showed minor Rouleaux formation in the vehicle control sample, which was not evident in the parallel treated P829 sample. There was no evidence of hemolysis nor was there evidence of protein precipitation in plasma or serum samples. All parameters remained within normal limits.

Sponsor's Conclusions: On the basis of these results Technetium Tc 99m P829 Injection prepared by reconstituting Kits for the Preparation of Technetium Tc 99m P829 with decayed generator eluate is compatible with human blood.

Reviewer's Comments: Agree.

R4.58 Perivascular Irritation Test. Study No. 96G-2380. [redacted] Dates, December 4-7, 1997. Report Dated December 24, 1996. Report Amended On November 17, 1997 and December 01, 1997. Lot Number 9609B02 (Final Formulation). In Compliance With GLP. Report In Volume 1.14, pp 277-296.

Design: This study was designed to assess the potential of Tc 99m P829 Injection to produce irritation following a single dose administered intradermally to the perivascular region of the marginal ear vein in the rabbit. New Zealand White rabbits were supplied by [redacted] [redacted] were 10-12 weeks of age and weighed 2.4-2.9 kg. The test material was supplied by the Sponsor to the test facility in 2 separate components; 1) Kit for preparation of Technetium Tc-99m P829, and 2) Decayed Tc-99m generator eluate. Just prior to dosing, the kits were reconstituted with decayed generator eluate and saline to yield concentrations equal to the recommended human dose. After reconstitution, the vials were heated in a boiling water bath for 10 minutes, then allowed to cool at room temperature for 15 minutes prior to dosing. Six rabbits (3 males and 3 females) received a perivascular injection of 0.25 ml of Tc 99m P829 Injection of 50 µg peptide/kg in the left ear. The right ear served as control and was injected with 0.25 ml saline. Rabbits were evaluated daily for clinical signs of toxicity and for erythema and edema at the injection site. Body weights were recorded prior to dosing and at termination. Three animals were terminated at 24 hours after dosing, and the remaining 3 animals at 72 hours after dosing. At necropsy the ears were evaluated for gross changes, followed by histopathological evaluation.

Results: All animals survived to scheduled termination, and there were no clinical signs of toxicity nor effects on body weight. No indications of erythema or edema were evident during the 24 or 72 hour observation period following dosing. Microscopic evaluation of the ear tissue did not demonstrate any Tc 99m P829 Injection-related changes. Both control and Tc 99m P829 Injection-treated ears demonstrated changes due to the trauma of injection, namely, leukocyte infiltration, and vascular congestion.

Sponsor's Conclusions: Tc 99m P829 Injection did not produce any irritation about the marginal ear vein following intradermal injection. Based on the clinical observations, macroscopic and histologic examinations, Tc 99m P829 Injection is considered a non-irritant.

Reviewer's Comments: Agree. There is no indication that Tc 99m P829 Injection induced irritation in the form of erythema or edema following perivascular injection near the marginal ear vein in the New Zealand White rabbit, and thus is not considered a perivascular irritant.

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TOXICOLOGY SUMMARY TABLE

Study Type	Species	Dose (µg Peptide/kg bd wt)	Dose Multiple to Human (m ² basis)	Study Duration	Major Finding
----- SINGLE DOSE -----					
R4.52 Final Formulation	Mice (Charles River, Swiss)	300 1000	25 83	14 d Obsn	Lethargy & piloerection seen in all animals, at both dose levels. No lethality or other signs
R4.50 Final Formulation	Rabbit (HRP, SPF-NZW)	200 600	67 100	14 d Obsn	NNF No lethality No treatment effects
----- MULTIPLE DOSE -----					
R4.54 Final Formulation	Rat (Charles River, SD)	40 100	6.7 17	14 d	NNF No lethality, no treatment effects
R4.57 Final Formulation	Rabbit (HRP, SPF-NZW)	40 100	13 33	14 d	NNF No lethality Females: Significant decrease in liver wt & liver/body wt ratio Males: Decreased liver wt & ratio but not significantly
----- SPECIAL TOXICOLOGY -----					
R4.59 Antigenicity	Guinea Pig	50	10	3/wk for 2 wks plus challenge	Not antigenic
R4.66 Micronucleus Test	Mice CD-1	1000 2000 4000	83 166 332	Single Dose Terminate at 72 hours	In all groups, for 1 hour after dosing, hypoactive, hunched posture, squinted eyes, and prostration. Not clastogenic
R4.58 Perivascular Irrit	Rabbit (NZW)	50 50	17 17	24 hours 72 hours	No irritation

Key: NNF = no noteworthy findings.

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35. OVERALL SUMMARY

PHARMACOLOGY SUMMARY

P829 is a synthetic 10 amino acid peptide comprised of a linear tetrapeptide attached to the side-chain of one of the amino acid residues of a cyclic hexapeptide. The cyclic hexapeptide domain contains the pharmacophore tyrosine-D-tryptophan-lysine-valine that binds to the somatostatin receptors. Somatostatin receptors have been identified in the central nervous system, the pituitary, pancreas, and the gastrointestinal tract. These receptors are overexpressed by neuroendocrine tumors and their metastases. Such expression of somatostatin receptor has been used as basis for diagnosis and therapy. The use of octreotide and ^{111}In -[DPTA]octreotide for treating hypersecretion of hormones symptomatic of carcinoid tumors and VIPomas, and for diagnostic purposes are pertinent examples. *The sponsor surmises that the high affinity binding of the technetium Tc 99m P829 will allow for the scintigraphic imaging of malignant tumors in the lung.*

The idea that a somatostatin receptor binding peptide can be used as an agent for the scintigraphic localization of primary and metastatic neuroendocrine tumors expressing somatostatin receptors is not new. As mentioned in the preceding paragraph, Octreoscan® Kit for the preparation of Indium In-111 Pentetreotide was approved on this basis. Therefore from a nonclinical pharmacology perspective, this summary will concentrate on examining the evidence provided by the sponsor to support the pharmacological basis of action, safety and efficacy of depreotide.

The sponsor is commended for the number of pre-clinical studies submitted to support the conceptual basis of this application. The results of several binding studies with human tumor cell lines indicate that technetium Tc 99m P829 binds with high affinity to somatostatin receptors on cell lines derived from human breast, SCLC, NSCLC, lymphoma, colon and pancreatic cancers. In one study, Technetium Tc 99m P829 bound with greater affinity to the small cell lung cancer cell line than to any of the other cell lines examined. These studies support the premise that technetium Tc 99m depreotide binds to somatostatin receptors on cell membranes since P829 and somatostatin-14 were equally effective at displacing specific binding on somatostatin receptor positive cell membranes. Furthermore, although SSTR2 appears to be the predominant SSTR subtype expressed by tumors, the results identified the SSTR2, SSTR3 (VIP-acceptor) and SSTR5, as the technetium Tc 99m P829 binding sites. Binding to SSTR3 (VIP-acceptor) site and the results indicating that Tc 99m P829 binding at this site, but not at SSTR2 and SSTR5 is displacable by VIP raises the possibility that injected Tc 99m P829 is capable of demonstrating activity at VIP sites in vivo. Whether this is possible at clinical relevant concentrations is not clear.

Whereas, both DPTA-octreotide and ^{111}In -[DPTA]octreotide have equivalent affinities for somatostatin receptor, ReO P829 has an affinity constant 30 times lower than P829 peptide. From a clinical perspective, the differences in affinity raises the possibility that co-injected P829

peptide will compete poorly with the ^{99m}Tc -P829 complexes for the somatostatin receptors thus allowing for the use of readily achievable specific activity. Studies were conducted with 85% and 94% RCP (relative chemical purity) to evaluate binding affinities of ^{99m}Tc -P829 complexes in the rat AR42J tumor membranes and in the rat AR42J and NCI-H69 human lung tumor xenografts. The results indicated that the 85% RCP P829 is as effective in somatostatin receptor binding as the higher purity 94% RCP material. Both the syn and anti isomers present in the injectate bind to the SSTR expressed in the AR42J tumor cell line with high (picomolar) affinity. The anti isomer, which is the principal isomer in the Technetium Tc 99m P829 injection, had the highest affinity for the SSTR. Pretreatment with octreotide greatly reduced uptake of the anti isomer, the syn isomer and Tc 99m P829.

A number of studies were conducted to evaluate the uptake of Technetium Tc 99m P829 injection by tumors known to express somatostatin receptors in vivo. These studies employed tumor models such as CA20948 pancreatic tumor-bearing Lewis rat, or Crl:Nu/Nu-nuBr nude mice inoculated with AR42J rat pancreatic tumor or inoculated with the NCI-H69 human lung tumor. Tumor uptake were demonstrated in all the models with good tumor:blood and tumor:muscle ratios. Technetium Tc 99m P829 binds with high affinity to somatostatin receptors in the Lewis rat model. Both the anti and syn isomers also bind to the receptors, but uptake was less for the isomers than with the complete formulation. Somatostatin receptor binding of both isomers and technetium Tc 99m P829 was blocked by pretreatment with octreotide.

Binding of technetium Tc 99m P829 to somatostatin receptor binding sites in excised human tumors previously shown to produced positive scintigraphic images in vivo supports a receptor-peptide interaction as a mechanism of somatostatin receptor binding by technetium Tc 99m P829. However, there is insufficient data with only 15 tissues imaged. Of these 15 tissues with positive technetium Tc 99m imaging, only 11 were positive for technetium Tc 99m P829 somatostatin receptor binding. Four tissues were either not detectable for somatostatin receptor binding of technetium Tc 99m P829 or were not done. While the technical challenges inherent in this type of experiment including inadequate sample material is noted, nevertheless one is concerned by the fact that some tissues were positive for Somatostatin-14 and/or Somatostatin-28 receptor binding but were negative for technetium Tc 99m P829. If true, the implication is that there is potential for imaging with technetium Tc 99m P829 to miss some somatostatin receptor bearing tumors.

No safety pharmacology study was conducted. The inhibitory influence of somatostatin and somatostatin analogues on arginine stimulated glucagon secretion was used as a physiologic parameter to measure the pharmacologic activity of P829 peptide. The glucagon response in pretreated male Sprague-Dawley rats at P829 peptide doses of 1 or 3 μg P829/kg resulted in no adverse effect on the post-prandial hormonal response. The NOEL for this study was 3-X MHD (by body weight). At 15 and 50 μg P829/kg, glucagon release was greatly reduced.

Taken together, the results are consistent with the premise that Tc 99m P829 binds to somatostatin receptors. It is the opinion of this reviewer that this product should identify somatostatin expressing tumors of any anatomical location, unless other factors preclude access to such a site. The data certainly support the narrow clinical indication of scintigraphic imaging of malignant tumors in the lung requested for by the sponsor.

PHARMACOKINETICS SUMMARY

The pharmacokinetic properties of Technetium Tc 99m P829 Injection have been described by an open two-compartment model in the rat, rabbit and rhesus monkey. Despite minor species differences in some parameters, Technetium Tc 99m P829 was rapidly cleared from the blood ($t_{1/2\alpha} = 2$ minutes). In all three species the volume of the central compartment exceeded the estimated blood volume, and the volume of distribution was in excess of the extra cellular fluid volume. The Technetium Tc 99m P829 was eliminated from the body ($K_{elim_half} = 12 - 22$ minutes) with a total clearance of 1-6 mL/min/kg. The pharmacokinetic properties were independent of dose as demonstrated by the blood elimination profiles for Technetium Tc 99m P829 Injection administered at 1 and 20 $\mu\text{g}/\text{kg}$ in the rat. Experimental renal dysfunction in the rat significantly reduced elimination. The kidneys were the major route of drug elimination, and in renal impairment/dysfunction there was no notable compensation by the hepatobiliary route of elimination in the rat. Technetium Tc 99m P829 was distributed principally to the kidneys, with >30% of the injected dose detected by 4 hours after administration. Distribution to other organs included the liver and gastrointestinal tract. The rabbit demonstrated uptake into the bone, including articulation sites of the shoulder and knee joints and the spine, with bone marrow concentration less than that at the articulation sites. This appears to be a finding specific to the rabbit. The pharmacokinetic properties and biodistribution of the unlabeled peptide component of Technetium Tc 99m P829 Injection was evaluated in the rat since 85% of a clinical dose of Tc 99m P829 Injection is unlabeled peptide. The peptide component as [$^3\text{H-Tyr}$]P829 exhibited pharmacokinetic properties similar to the technetium-labeled P829. The biodistribution of the [$^3\text{H-Tyr}$]P829 to the major organs was qualitatively and quantitatively similar to the distribution of Tc 99m P829. A minor difference was the greater amount of the [$^3\text{H-Tyr}$]P829 found in the liver at 4 hours compared to the Tc 99m P829.

Based on the review of the pharmacokinetic human data, the pharmacokinetic properties of Technetium Tc 99m P829 Injection have been described by an open three-compartment model in the human. Where appropriate, comparative data are shown in the following table.

Comparative Pharmacokinetic Parameters for Technetium Tc 99m P829 Injection in the Rat, Rabbit, Monkey and Normal Human

Parameter	Rat (M/F) (n = 13)	Rabbit (n = 3)	Monkey (n = 1)	Human (n=9)
C_{60} (%ID/g)	1.99 ± 0.55	0.313 ± 0.05	0.199	
V_c (mL/kg)	303 ± 92	139.5 ± 9.3	100.5	
$t_{1/2\alpha}$ (min)	1.92 ± 0.44	2.4 ± 0.8	1.6	4.3 ± 2.0
$t_{1/2\beta}$ (min)	33.0 ± 7.9	60.7 ± 6.0	67.4	43.6 ± 11.5
$t_{1/2\gamma\beta}$ (hr)				22.4 ± 11.0
$AUC_{t_0-240 \text{ min}}$ (% ID•min/g)	35.8 ± 8.3	9.6 ± 2.2	5.63	
V_{Dss} (mL/kg)	732 ± 183	368.1 ± 24.0	329.4	1560 ± 850
$K_{elim \text{ half}}$ (min)	12.3 ± 3.5	21.6 ± 4.3	19.3	
Cl_{tot} (mL/min/kg)	6.2 ± 1.2	1.83 ± 0.4	1.03	2.12 ± 1.3

Biodistribution of Technetium Tc 99m P829 Injection as Percent Injected Dose in the Rat, Rabbit, Monkey

Tissue	Rat 4 Hours	Rabbit 1.5 Hours	Monkey 4 Hours
Kidney	38.4 ± 7	32.4 ± 1.2	40
Liver	10.33 ± 4.4	7.1 ± 0.3	10
G.I. Tract	2.43 ± 0.64	12.1 ± 2.2	-
Spleen	0.37 ± 0.13	0.13 ± 0.09	-
Carcass	7.4 ± 3.3	-	-
Urine	25.8 ± 8.7	9.4 ± 4.6	32

Single Dose Toxicity

Intravenous single dose toxicity studies with the final formulation of technetium Tc 99m depreotide were conducted in albino Swiss mice and albino SPF-NZW rabbit. No deaths were observed in either species, even at the highest dose of 1000 μg peptide/kg in the mice and 600 μg peptide/kg in the rabbit. The only treatment effects seen in the mice were lethargy and piloerection, which cleared within 24 hours, seen in all animals treated with technetium Tc 99m depreotide at dose levels of 300 and 1000 μg peptide/kg. No necropsy effects or histopathology of liver, spleen, lung, heart or kidney were seen. There were no effects seen in the rabbit study even at the highest dose of 600 μg peptide/kg.

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Repeat Dose Toxicity

Sprague Dawley rats, 10/sex/group, received daily intravenous injections of the original formulation and final formulation at the highest dose of 100 μg peptide/kg for 14 days. There was no lethality and no treatment-related effects seen in either study. On a body surface area basis this is a multiple of the human dose of 17x for each daily dose.

In two separate 14-day rabbit studies, the high dose level of 100 μg peptide/kg/day was administered. On a body surface area basis this is a multiple of the human dose of 33x for each daily dose. One study was conducted with the original formulation and the other with the final formulation. In the study with the final formulation, females at the highest dose of 100 μg peptide/kg exhibited significantly decreased absolute and relative liver weights. The values for males were also decreased, but not significantly. There was no lethality in either study, and there were no other effects seen in either study.

Carcinogenicity: Long term animal studies were not conducted.

Immunotoxicity

In a systemic antigenicity study in guinea pigs, there was no indication of anaphylactic responses, and therefore it is concluded that technetium Tc99m depreotide is not a systemic antigen in guinea pigs.

Reproductive and Developmental Toxicity: Studies not conducted

Genetic Toxicity

The appropriate genotoxicity tests were conducted, according to the ICH guidelines, on the peptide P829 and on the kit for preparation of technetium Tc99m depreotide. Test results were negative for genotoxicity in the following: 1) Ames bacterial assay with and without S9 activation, with *S. typhimurium* and *E. coli*, 2) Bone marrow erythrocyte micronucleus assay in Swiss Webster mice, 3) Mutation assay at the thymidine kinase locus in cultured L5178Y mouse lymphoma cells with and without S9 activation.

Special Toxicity

Technetium Tc 99m P829 was found to be compatible with human blood at dilutions of 1:8 and 1:4 in whole blood. Effects on hematologic parameters including hemolysis and Rouleaux formation were not observed. No irritation as evidenced grossly by edema or erythema or histopathologically were observed in the rabbit perivascular irritation study.

Nonclinical Pharmacology/Toxicology Concerns

1. Analysis of dosing solutions: The dosing solutions used in the GLP pivotal toxicology studies were not analyzed for concentration of test material. The GLP regulations require that a representative number of dosing solutions be analyzed to ensure content. The Sponsor provided the Certificate of Analysis for the kit for preparation of technetium Tc 99m P829 to the performing laboratories, however, the laboratory indicated that analysis of dosing solutions was the responsibility of the Sponsor. This data was not included in the submission. The Sponsor was asked to provide this information, however in a subsequent submission, the Sponsor indicated that dosing solutions were not analyzed and that formulations records at the contract laboratories would document the content of dosing solutions. Copies of the formulations records will be requested from the Sponsor.

2. Heating of dosing solutions: In all of the nonclinical studies with the kit for preparation of technetium Tc99m depreotide, the kit was reconstituted and heated in a water bath for 10 minutes and cooled to room temperature prior to dosing. However, in some of the clinical trials, the reconstituted dosing solutions were administered to subjects without first being heated. This is of utmost concern, since there is no nonclinical safety data to support administration of the drug prepared in this manner.

36. RECOMMENDATIONS:

Internal Comments: From the standpoint of nonclinical pharmacology and toxicology, the NDA 21012 is approvable when the Sponsor addresses the deficiencies listed below. Dosing solutions were not analyzed as required by GLP's, however formulations records may adequately document the content of the dosing solutions used. The Sponsor will be requested to provide copies of the formulations records of the studies listed below.

Future review issues**External Recommendations (to Sponsor)**

Dosing Solutions: Please provide copies of formulations records for the dosing solutions in the pivotal GLP nonclinical toxicology studies with reconstituted technetium Tc 99m P829. Study Numbers included are: R4.50, R4.52, R4.53, R4.54, R4.56 and R4.57.

37. NDA ISSUES:

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LABELLING

39. INVESTIGATOR'S BROCHURE/INFORMED CONSENT REVIEW: None.

40. REVIEWER'S SIGNATURE:

Pharmacology Section:

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David E. Bailey, Ph.D.

November 16, 1998

Date

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Adebayo A. Laniyonu, Ph. D

11/16/98

Date

TEAM LEADER CONCURRENCE:

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Laraine L. Meyers, R. Ph., Ph.D.

16 November 1998

DATE

40. CC: LIST.

- ORIGINAL, NDA#21-012
- HFD-160
- HFD-160/PHARM/BAILEYD/MEYERSL/LANIYONUA
- HFD-160/CSO/COLANGELOK
- HFD-160/MO/LOEWKES
- HFD-160/CHEM/HARIPINHALLIR
- HFD-160/STATS/
- HFD-160/BIOPHARM/CHOI
- HFD-345/VISWANATHAN

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ON ORIGINAL

41. Appendix

42. Draft Date:

September 5, 1998.

Revision Dates:

October 2, 1998

November 16, 1998

43. Addendum