The University of Michigan
Medical Center
Ann Arbor, Michigan 48109-0028

Department of Internal Medicine
Division of Nuclear Medicine
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(313) 936-5090

Names of parties and certain other identifying details have been removed in order to prevent a clearly unwarranted invasion of the personal privacy of the individuals involved.

October 13, 1989

Mr. Roy Caniano
United States Nuclear Regulatory Commission
799 Rooseveldt Rd.
Glen Allan, Ill. 60137

Dear Mr Caniano:

This letter supplements our previous telephonic discussions over the last few weeks concerning the treatment of [redacted] (University of Michigan registration # [redacted] with 131 I Metaiodobenzylguanidine (MIBG) for end stage neuroblastoma.

The most detailed protocol is that in the IND document which was submitted to and approved by the Food and Drug Administration. I enclose a photocopy of this very detailed protocol. You will note that I have tabbed the documents at the page which specifies the dose and highlighted the relevant paragraph. Note the dose is 1-4 doses of up to 200mCi even though these are pediatric patients. You will also find attached the various approvals relating to this protocol (tabbed).

You will note that I have enclosed photocopies of the prescriptions and dispensing records for the doses administrated to [redacted] which were: 9-16-85 203mCi, 1-14-86 216mCi, 2-25-86 220mCi. The dispensed doses are thus within 10% of the prescribed dose which was 200mCi in every instance. It should be further be noted that the therapy dose is infused through a long infusion system with several 3-way taps and previous measurements indicate that about 5-7% of the dispensed dose adsorbs to the plastic ware. Thus I feel that the dose administer undoubtly is within that of the written protocols.

I would also draw you attention to the attached reprints which indicate that the doses used are in line with those being used by other research groups attempting similar therapies.

I hope that you find this fully satisfactory, if you require further details please feel free to contact me at the above address or (313) 936-5305.

Sincerely,

B. Shapiro, M.B., Ch.B., Ph.D.
Chairman, Subcommittee on the Human Use of Radioisotopes
Professor of Internal Medicine

BS/db

Sisson/Shapiro 80-123

THE UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
ANN ARBOR, MICHIGAN 48109

DEPARTMENT OF INTERNAL MEDICINE
Division of Nuclear Medicine

June 21, 1984

William J. Gyarfas, M.D.
Director, Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Gyarfas:

Please amend our I.N.D. #17,239 to include the following indication for the administration of ^{131}I-meta-iodobenzylguanidine (^{131}I-NP-292).

X. Proposed Clinical Study: High Activity ^{131}I-meta-iodobenzylguanidine for the Treatment of Neuroblastomas

A. Objectives: Treatments with ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG), through radiation effects, will reduce the size and function of metastatic deposits of neuroblastomas without producing adverse or harmful effects.

B. Rationale

Neuroblastoma is the second most common solid tumor in childhood and accounts for 15% of cancer deaths in children [1]. Modern chemotherapies coupled with external beam irradiation have increased survival times, but the prognosis for affected patients, and especially those beyond two years of age at diagnosis remains grim [2]. The responses to external beam irradiation have often bee striking, but the complications from this form of treatment have been so severe that doses have been purposely kept low [2]. There is then a need for a more effective therapy for neuroblastoma, a tumor that is so devastating to our young.

Dr. Donald Wieland of our Nuclear Medicine Division synthesized I-131 metaiodobenzylguanidine to locate pheochromocytomas [3, 4]. This radiopharmaceutical has succeeded amazingly well to uncover even the most elusive pheochromocytomas [5-8]. In our diagnostic endeavors, it became clear that I-131 MIBG reached such high concentrations in some malignant pheochromocytomas that therapeutic irradiation could be delivered by 100-200 mCi of the agent [9]. Thus, we have now given I-131 MIBG as treatment to 16 patients; of the 12 who have been evaluated for results, 5 have shown marked subjective (disabling symptoms disappeared) and objective (diminution in size and function of tumors to less than one half pre-therapeutic values) benefits [10-12 and Appendix A]. Thus, I-131 MIBG has been shown to be of distinct therapeutic value to some patients with pheochromocytoma, an adrenergic

tumor. Subsequently, neuroblastoma, another adrenergic tumor, has been found to concentrate I-131 MIBG [13-15a, 15b]. We have heard from two separate groups of investigators that I-131 MIBG in therapeutic doses of 20-120 mCi has brought about dramatic remissions in six children beyond two years of age with stage IV (metastatic to bone) neuroblastoma [15b, 16]. The remission has been sustained beyond two years in at least one patient [15b].

Uptake and retention of I-131 MIBG is dependent upon, among other factors, the presence of adrenergic storage vesicles [3]. In fully developed adrenergic tissues, the membranes of these vesicles contain dopamine beta hydroxylase which converts dopamine to norepinephrine. Neuroblastomas may contain vesicles and exhibit varied levels of function, secreting dopa, dopamine and at times norepinephrine.

When considering treatment of neuroblastoma it is important to recognize that prognosis is correlated with the presence of vesicles [17] and the degree of function [18-20]. Also, the levels of serum neuron-specific enolase appears to predict outcome of patients [21]. In proposing a new therapy, such as I-131 MIBG, for neuroblastoma, it is essential to identify predictors of the natural course of the disease, so that the group under new treatment can be compared with a appropriate group under conventional therapy.

Since the irradiation from a radiopharmaceutical is largely confined to the tumor [22], treatment of neuroblastoma with I-131 MIBG may deliver much more irradiation (over 5000 rads) to the tumors than can be given by external beam, yet cause none of the serious side effects that have been associated with irradiation of the past [2]. Since neuroblastomas have been sensitive to irradiation (much more so than malignant pheochromocytomas), the delivery of over 5000 rads to all tumors in a patient could effect a cure. Remarkably high tumor uptakes of tracer doses of 131-I-MIBG have been recorded (40% of administered dose) (13).

In summary, treatment with I-131-MIBG is a new approach with great promise for patients afflicted with a devastating cancer, neuroblastoma.

C. Preliminary Data

We have performed scintigraphy with tracer doses of I-131 MIBG in 7 patients with neuroblastoma. The uptake of I-131 MIBG by the tumors was absent in 3, weak in 2, moderate in 1, and intense in one patient. Images of the child with the intense uptake are shown in Figure 1 and can be compared with comparable images made with the standard bone scanning agent seen in Figure 2. Although dosimetry was not performed, our experience with malignant pheochromocytomas leads us to believe that uptake and retention of I-131 MIBG in this patient would translate into over 2000 rads per 50 mCi dose.

Copies of our articles on the treatment of malignant pheochromocytomas are enclosed in the Appendix. Also enclosed is the abstract on the same subject, and a copy of the paper as read (along with reproductions of slides) at the Society of Nuclear Medicine Annual Meeting in Los Angeles on June 8, 1984. These articles demostrate our knowledge and experience in using I-131 MIBG as a therapeutic radiopharmaceutical.

A 14 month old girl developed a tumor above her left eye over a few weeks. Histology of the tumor showed neuroblastoma in mid-May, 1984. Computed tomography demonstrated the tumor to be extending medially and inward. The primary tumor was located in the region of the right adrenal gland by ultrasound. She was then evaluated by scintigraphic techniques.

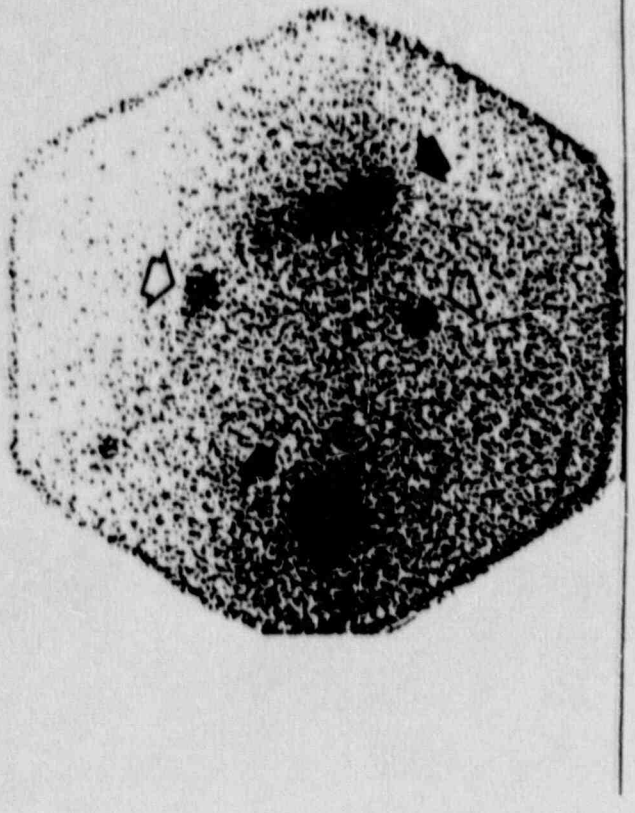

Figure 1A - Images made 3 days after 0.12 mCi of I-131 MIBG.

The orbital tumor and its medial extension and the abdominal tumor. (Closed arrows point to tumors, open arrows point to markers.)

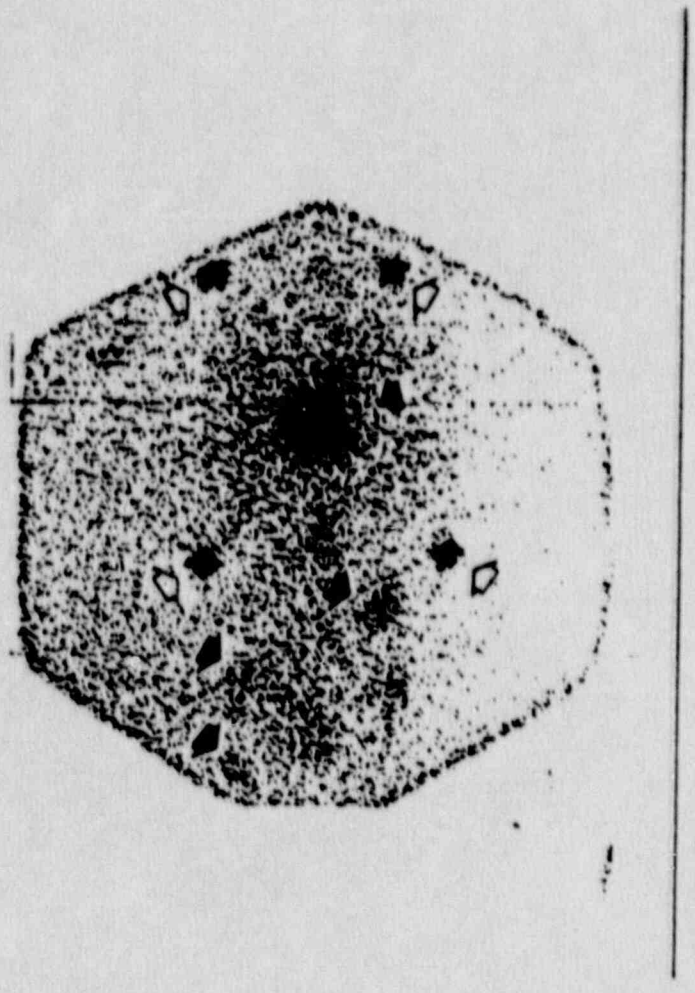

Figure 1B - Images made 3 days after 0.12 mCi of I-131 MIBG.

The abdominal tumor is again seen in a lower view; there are also probable metastases in her femurs that were not seen on skeletal images. (Closed arrows point to tumors, open arrows point to markers.)

Preliminary estimates of the uptake and retention (excellent at 4 days) suggest that the neuroblastoma in this child could receive therapeutic irradiation from 50 mCi of I-131 MIBG. Treatment with I-131 MIBG will be considered after a conventional course of chemotherapy and external beam irradiation.

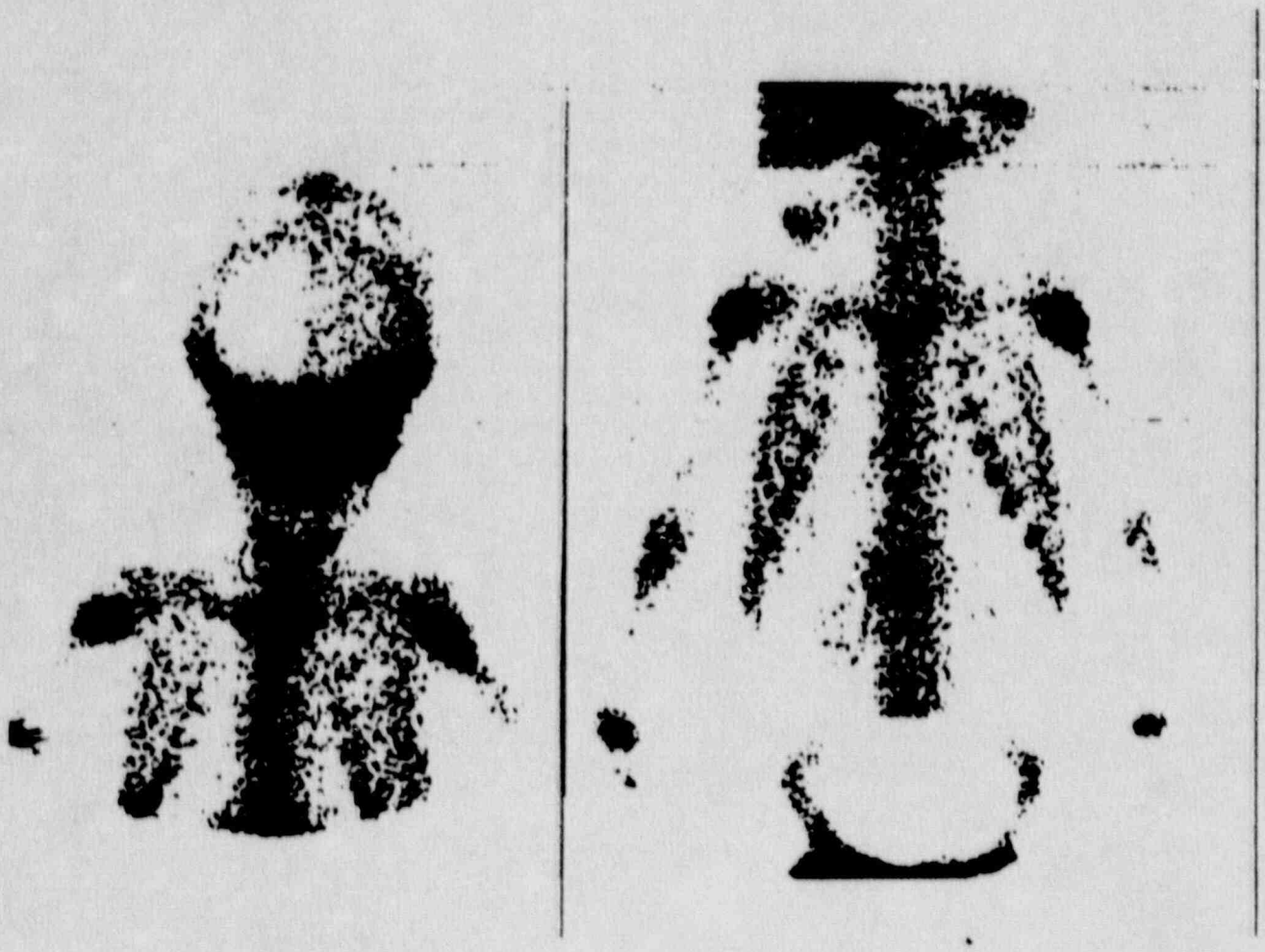

Figure 2 - Skeletal images made with Tc-99m methylene diphosphonate. The orbital tumor involves bone, as probably does the abdominal tumor.

D. Experimental Design

1. Patients

Patients will be referred for study and treatment to the Oncology Division of the Department of Pediatrics. Dr. Raymond Hutchinson of the Department of Pediatrics will coordinate patient care.

Diagnosis will be established by clinical features and morphology of a tumor biopsy. Electron microscopy will be carried out on all specimens, and the presence number of adrenergic vesicles will be determined and their number estimated [17].

Because I-131 MIBG treatment is investigational and has now uncertain efficacy, conventional treatment with external beam irradiation and chemotherapy will be instituted promptly after diagnosis. If the conventional treatment(s) fail to achieve substantial benefit within four weeks, the possibility of I-131 MIBG will be investigated.

We currently see about 12 patients per year with neuroblastoma at the University of Michigan Medical Center. Estimating from our initial experience two-to-three of these patients would be candidates for treatment with I-131 MIBG. However, a new therapy for a lethal disease should attract additional referrals from across the country. Since I-131 MIBG is now available to most medical centers for diagnosis (but not therapy), preliminary studies at referring hospitals would select patients who would be the most likely candidates for therapy with I-131 MIBG. Thus, with new referrals, we believe we will treat about 20 patients each year.

2. Investigations preliminary to I-131 MIBG therapy.

If conventional treatment(s) have failed to achieve substantial benefit then the following tests will be done.

a. A urine specimen (12 hours where possible) will be collected and measurements will be made for:

dopamine [23];
norepinephrine,
epinephrine,
nometanephrine,
metanephrine, and
vanilmandelic acid (VMA) [24]; and
homovanillic acid (HVA) [25].

Values will be expressed per gram creatinine.

b. A blood specimen (8 ml) will be obtained via an indwelling needle while the patient is rested and recumbant for 30 minutes for measurements of

dopamine,
norepinephrine, and
epinephrine [23]; and
neuron-specific enolase [21].

c. Scintigraphy with I-131 MIBG will be by our standard procedures using 0.5 mCi/1.7 m^2 of body surface area [25]. Thyroid uptake of I-131 will be suppressed by the administration of 1 drop per day of saturated solution of potassium iodide; if I-131 MIBG treatment is given, potassium iodide will be continued for a total of six weeks.

Bone scintigraphy using Tc-99m methylene diphosphonate will be an adjunct in determining the extent of disease.

Scintigraphy will include conjugate views (180° opposed) of tumors and will be repeated daily over six days to enable calculation of the I-131 MIBG uptake into, and rate of disappearance from individual tumors [10, 11]. Ultrasound or computed tomography will determine volumes of selected tumors. Then rad dose per millicuries of I-131 MIBG will be calculated for one or more tumors [10, 11].

Rates of urinary excretion of radioactivity will be measured over four days to enable estimates of whole body rad dose [10, 11].

3. Treatment with I-131 MIBG

If a single dose of I-131 MIBG will impart over 2000 rads to the tumors of the patient, treatment will be given. Generally, individual doses will not exceed 200 mCi and will be in proportion to body weight when the weight is less than 55 Kg. The whole body dose will not exceed 50 rads.

Two-to-three treatments will be given if more irradiation is required to reduce tumor size and there have been no adverse effects to the treatments. We aim ultimately to exceed 5000 rads to the tumor. I-131 MIBG will be prepared in high specific activity so that 1 mCi contains less that 0.03 mg of the radiopharmaceutical. Infusion over 30 minutes will ensure safety. Blood pressure and heart rates will be monitored during and for one hour following infusions. Patients will be isolated (private room) until their retention of radioactivity is less than 30 mCi (measured by external monitors).

4. Evaluations

a. Safety Evaluation - Acute:

1) Patients will be confined to a private room (Clinical Research Unit, University of Michigan) as long as radiation hazards persist. All radiation safety precautions routinely observed for ^{131}I-thyroid therapies will be adhered to. Patients will be hospitalized and under surveillance for at least 7 days after therapy (radiation hazards should be minimal at 3-4 days.

2) Vital Signs: (see Appendix D: ^{131}I-MIBG Therapy Case Report Form).

(i) Blood pressure will be monitored every 5 mn. during infusion of the ^{131}I-MIBG and regularly thereafter using an automatic device (Arteriosonde).

(ii) Heart rate will be continuously monitored during ^{131}I-MIBG infusion (EKG and Arteriosonde) and regularly thereafter.

(iii) Respirations and temperature will be monitored preinfusion and at 1 and 4 hours post-infusion.

c) Adverse Effects: Medications (propanolol, phentolamine, sodium nitroprusside) to counteract sudden changes in heart rate and blood pressure will be immediately available. An intravenous line will be kept open during and for at least 24 hours after infusion of the ^{131}I-MIBG. All adverse reactions will be indicated on the ^{131}I-MIBG Therapy Case Report Form (see Appendix D).

d) Clinical Blood and Urine Testing: To evaluate the possibility of acute adverse effects:

(i) Routine urinalysis will be obtained within 48 hours pre-injection and at 48 hours post-injection.

(ii) Determination of serum BUN, SGOT, alkaline phosphatase, LDH, CPK, creatinine, phosphorus and bilirubin will be performed within 48 hours pre-injection and at 48 hours post-injection.

(iii) Complete blood counts will be obtained within 48 hours pre-injection and at 48 hours post-injection. All values (including normal values for this institution if value is abnormal) will be indicated on the ^{131}I-MIBG Therapy Case Report Form (see Appendix D).

b. Search for benefical effects.

1) Clinical evaluations will be bi-weekly after treatment and well-being and disabilities will be graded. Palpable and visible tumors will be measured.

2) Biochemical indices (blood and urine -- see above) will be repeated at 8 and 16 weeks. Also at these times tumor size will again be measured by ultrasound or computed tomography.

3) At 16 weeks after treatment, diagnostic scintigraphy will be repeated. Decision for retreatment will be made if

a) Additional irradiation would appear to be beneficial (again we will try to exceed a total of 5000 rads to the tumors);

b) No serious untoward effects were seen (see below); and

c) The tumor will still receive over 2000 rads (while total body dose is less than 50 rads) from the planned dose.

4) Survival, and especially tumor-free survival, times will be our major index of success.

Additional Evidence of success will be:

(i) a reduction in plasma hormone levels and urine hormone excretion to at least 50% of the mean pretreatment levels (3 values when measured 3 times over a one-month interval.

(ii) a significant reduction in the size of the largest and/or most dangerous tumor(s) on radiography or clinical examination by standardized criteria (16).

c. Search for untoward effects.

1) In our experience, the bone marrow is at greatest risk from irradiation by I-131 MIBG. Complete blood counts, including platelet counts, will be made before and at 2, 4, 8 and 16 weeks after treatment.

2) At some risk are the thyroid gland (from I-131 release from I-131 MIBG) and the adrenal cortex (from I-131 MIBG concentrated in the adrenal medulla) so TSH, ACTH and cortisol will be measured before and 16 weeks after treatment.

d. Analysis

1) Survival will be compared with published results [1, 17-21].

2) Correlations of survival times will be made with the results of

a) Presence of adrenergic vesicles

b) Secretion of catecholamines in blood and urine

c) level of neuron-specific enolase in plasma.

3) Patients will be observed for any evidence of autonomic neuropathy: cardiovascular instability (in blood pressure and heart rate and rhythm), gastrointestinal malfunction and urinary malfunction.

V. Methods, Facilities and Controls Used for the Synthesis, Processing and Packaging of ^{131}I-MIBG for Therapy Studies (Note: this radiopharmaceutical will be synthesized for use by the physician sponsor only. It will not be manufactured for distribution to other clinical investigators.)

A. See Appendix E of this notice for the revised synthesis of ^{131}I-MIBG for Therapy Studies. Note that we will limit the amount of "cold" meta-iodobenzylguanidine utilized in the synthesis to 5 ± 1 mg; thus minimizing the risks of pharmacologic/adverse reactions. (See toxicity data submitted in the original I.N.D. #17,239.)

Two minor revisions in the synthesis include the substitution of ammonium sulfate (8 mg) for ammonium dihydrogen phosphate as the buffer and the addition of benzyl alcohol (1%) as a free radical scavenger/stabilizing agent. See Appendix F for letters certifying the specifications of these reagents. The toxic potential of these components is negligible. The LD50 of ammonium sulfate in mice is 610 mg/kg following intraperitoneal administration (Registry of Toxic Effects of Chemical Substances, 1978, Dept. of Health, Education and Welfare, p. 103); representing a margin of safety of greater than 5000 for this formulation. Benzyl alcohol is commonly used as a bacteriostatic agent (1%) in Bacteriostatic Normal Saline, U.S.P. All other portions of this section remain unchanged.

B. Process Controls (See I.N.D. #17,239):

1) ^{131}I-Meta-iodobenzylguanidine sulfate

a) Non-radioactive meta-iodobenzylguanidine - no changes.

b) ^{131}I-meta-iodobenzylguanidine

(i) Radiochemical purity - no changes

(ii) Radionuclidic purity - no changes

(iii) pH - no changes

(iv) Visual inspection - no changes

(v) Sterility testing - no changes

(vi) Pyrogen testing - no changes

(vii) Radioassay - Release specifications

Specific activity: ≥ 20 mCi/mg at calibration time immediately post synthesis

Specific concentration: ≥ 3 mCi/ml at a calibration time immediately post synthesis

Total radioactivity: ≥ 100 mCi at a calibration time immediately post synthesis

2)-4) No changes

C. Stability of ^{131}I-meta-iodobenzylguanidine for Therapy: The therapy ^{131}I-MIBG will be administered as soon as possible after synthesis and quality control procedures. Preliminary stability studies on lower activity ^{131}I-MIBG indicate stability for at least 14 days (see original I.N.D. #17,239 and supplemental information). A 24-hour maximum expiration time will be placed on the ^{131}I-MIBG for therapy.

D. Packaging and storage:

1) No changes

2) Labeling

a) Immediate container label:

[redacted]
EXPIRES - time/date
I-131-meta-
odobenzylguanidine
THERAPY-Patient Name
Date of Therapy
Synthesis
Caution: Investigational
Drug-Limited Use Only
Act time Date/
Init

b) Outer container (lead pig) label:

Rx Number
Patient Name
I-131-MP-2 (mIBG)
SPECIAL THERAPY STUDY
Investigational Use
Only
Act. time Date/
Init

E. No changes

F. No changes

Respectfully submitted,

William H. Beierwaltes, M.D.
Physician Sponsor, I.N.D. #17,239

James C. Sisson, M.D.
Co-Investigator

Brahm Shapiro, M.D.
Co-Investigator

James C. Sisson, M

SOCIETY OF NUCLEAR MEDICINE MEETING
Endocrine II Session
June 8, 1984

As a preliminary to my discussion of treatment of malignant pheochromocytomas a brief review of pharmacology is necessary. [SLIDE 1]

This is the formula for meta-iodobenzylguanidine or MIBG, here labeled with iodine-131. [redacted] of adrenergic [redacted] phrine and [redacted]

Norepi[redacted] in vesicles [redacted] by the adrenergic tissues in a process that is regulatory for the tissue, and conservatory of norepinephrine. MIBG enters adrenergic tissues, including pheochromocytomas, by this uptake pathway. And MIBG, like norepinephrine, is stored in vesicles. However, MIBG is taken up in small quantities and retained only briefly by normal adrenergic tissues. On the other hand, some pheochromocytomas exhibit a marked avidity for MIBG and retain the radiopharmaceutical with a biologic half-life that exceeds 2 days. Such uptake and retention enables therapeutic amounts of radiation to be delivered to these pheochromocytomas by 100 mCi or more of I-131 labeled MIBG within the tumors. [SLIDE 3]

The method of treatment is shown in this slide (see content of Slide 3). Radiation dosimetry made use of computed tomography for tumor volumes, and the conjugate view method for quantifying radioactivity. MIBG is prepared in high specific activity. Initially we gave 100 mCi, but subsequently 200 mCi has become our standard dose whenever this quantity can be prepared. As a precaution against any pharmacologic effects from even this small quantity of MIBG, the dose is infused over 90 months. [SLIDE 4]

Our ability to treat patients led to these hypotheses or goals (see content of Slide 4).

Responses of 10 Patients with Malignant Pheochromocytomas to ^{131}I-MIBG Therapies

Pt.	Age	Sex	^{131}I-MIBG Rx		Complications	Overall Status		
			No. of doses	Cumulative mCi		Symptoms	Catecholamine Excretion*	Size† of Tumors*
1.	61	M	5	623	None	Disappeared; no therapy now	<0.5 (normal except for metanephrines)	<0.3 (retroperitoneal recurrence on scintiscan regressed after fifth Rx
2.	66	F	4	573	Died of non-hemorrhagic stroke when normotensive	Disappeared; Minimal blockade‡		<0.3 (in liver)
3.	26	M	3	410	Temporary alopecia over tumor in skull	None on blockade‡		Unchanged (in bone)
4.	33	M	3	480	None	None on blockade‡		Unchanged (in bone)
5.	45	M	3	493	Transient leukopenia	None on blockade‡ but higher		Increased (in retroperitoneum and bone) after 3rd Rx
6.	42	M	2	366	Persisting leukopenia (2000-2500 mm^3)	Disappeared		Uncertain (in bone)
7.	36	M	2	374	None	Recurrent attacks unchanged		Unchanged (in retroperitoneum)
8.	26	F	1	130	Transient pain over tumor	None on blockade‡		Unchanged (in liver)
9.	37	F	1	208	None	Disappeared		Uncertain (in bone)
10.	30	M	1	186	None	Increased; given chemotherapy Rx		Progressed (in retroperitoneum)

* Fraction of pretherapeutic measurement
† By x-ray or transmission computed tomography
‡ Phenoxybenzamine and propranolol

1984 Abstract Form for Scientific Papers and Scientific Exhibits
Society of Nuclear Medicine 31st Annual Meeting
Los Angeles, California, June 5-8, 1984

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Abstracts will Be Published As Typed

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TYPE ABSTRACT HERE: (BE SURE TO STAY WITHIN BORDER)

^{131}I-METAIODOBENZYLGUANIDINE TREATMENT OF MALIGNANT PHEOCHROMOCYTOMAS.

J. Sisson, B. Shapiro, J. Glowniak, W. Beierwaltes, T. Mangner, D. Wieland, J. Carey, N. Petry, J. Copp, P. Eyre. University of Michigan, Ann Arbor, MI.

When ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) concentrates in malignant pheochromocytomas, therapeutic radiation can be delivered from within these tumors [illegible] oped a new tumor on scintigraphy; a fifth treatment caused regression of the new abnormality and preserved the attained benefits. The other 3 patients have shown little or no response despite additional (third) treatments in 2.

Three of the next 5 patients have responded beneficially to ^{131}I-MIBG. One (208 mCi) and two (197 & 169 mCi) doses in separate patients resulted in: disappearance of symptoms and a diminution of catecholamine excretion (by more than 50% in one and to almost normal levels in the other); but the boney sites made changes in volume of tumors difficult to measure. In an asymptomatic patient, 130 mCi reduced her catecholamine excretion by 33%, but volumes of her liver tumors remain unchanged as yet. One patient had no change after two doses (207 & 167 mCi), and one patient's disease progressed unabated after 186 mCi.

In addition to uptake and retention of ^{131}I-MIBG by tumors, other factors must also determine responses. Moderate leukopenia in two patients has been the only adverse effect. We conclude that ^{131}I-MIBG offers hope to patients with heretofore resistant malignant pheochromocytomas.

Please check one box for each of the following statements:

1. This abstract represents:
   - [X] a scientific paper (oral or poster presentation)
   - [ ] a scientific exhibit (by slide, viewbox or freestanding display)
2. I am willing to present this paper:
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   - [ ] either orally or by posterboard
   - [ ] by posterboard only
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TYPE FULL NAME OF AUTHOR PRESENTING PAPER: James C. Sisson, M.D.

List the name, address, and telephone number of the principal author who should receive all correspondence.

Name James C. Sisson, M.D.

Institution University of Michigan Medical Center

Division or Dept. Nuclear Medicine Div., Box 021

Street 1405 E. Ann St.

City Ann Arbor State MI Zip 48109

Phone Number (313) 763-3403

DEADLINES

For Scientific Papers: Abstracts must be received (not postmarked) by Thursday, January 12, 1984.
For Scientific Exhibits: Abstracts must be received (not postmarked) by Thursday, February 23, 1984.

CONSENT FORM

FOR A [redacted]

A. General Information

The tumor that you/your child has, neuroblastoma, is situated in your/his/her body so that it cannot be removed by an operation. Drugs and radiotherapy that are often given to patients with tumors such as this have not been helpful.

[redacted]

Treatments of an overactive thyroid gland and of thyroid cancer with radioactive iodine (^{131}I) have produced remarkable results in terms of reducing secretion of hormone, and shrinking of tumor.

Radioactive iodine can be taken into the tumor by attaching it to a certain drug, abbreviated ^{131}I-MIBG. The goals of this treatment will be the same as those achieved with thyroid diseases:

Shrinking of tumor.
Reducing secretion of hormone.

Preliminary studies indicate that ^{131}I-MIBG will enter the tumor in sufficient quantity so that the radiation from ^{131}I will produce a beneficial effect. It appears that no other tissue or organ in the body will receive a dangerous level of radiation from such a treatment. Preliminary results with ^{131}I-MIBG in pheochromocytomas (a tumor related to neuroblastoma) have been encouraging.

B. The Methods Used

1. Preliminary studies using a small or tracer quantity of ^{131}I-MIBG have already been carried out. They have demonstrated that the ^{131}I-MIBG enters the tumor, but does not accumulate to dangerous levels in other organs. The tests also indicate the amount necessary for therapy.

2. You/Your child will be given the therapy dose of ^{131}I-MIBG intravenously over about a 30-minute period.

3. You/Your child will remain in the Clinical Research Center for one week. During that time the blood pressure and heart rate will be frequently monitored. We will periodically examine you/him/her. By the end of that time you/he/she will have very little radioactivity left in the body.

4. At the end of one week and every two weeks for three months thereafter we will reexamine you/your child for changes in blood pressure and well being. We will also measure the hormone levels in the blood and urine.

5. At the end of four months we will again examine you/your child, measure the hormone levels in the blood and urine, and take new x-rays of the tumor. Another scan with a tracer quantity of ^{131}I-MIBG will be performed.

6. If indicated, [redacted] as before.

7. We will reevaluate you/your child every 4-6 months after treatments have ceases.

C. Risks and Possible Benefits

1. The risks of the treatment are three. [redacted]

   a. Radiation from any source, including that from ^{131}I-MIBG, could damage organs in you/your child's body such as the bone marrow; even induce cancer. From our experience with ^{131}I in the treatment of thyroid diseases, we believe that organ damage and the development of cancer are most unlikely. Moderate depression of white blood cell numbers has been the only side effect thus far encountered. This may be associated with an increased risk of infection.

   b. It is possible that the radiation from ^{131}I-MIBG could damage some of the nerves controlling the blood vessels. The blood pressure could then become low, making it difficult for you/your child to stand up without being dizzy. Again, we believe this to be an unlikely consequence.

2. The possible benefits of the treatment are two.

   a. The radiation could stop the growth of the tumor, even cause the tumor to shrink and die. This effect should be apparent in 4-12 months.

3. The treatment with ^{131}I-MIBG may not work. However, the only alternative is to continue with the treatment you/your child has been receiving.

D. Your Rights and Privileges

You should feel free to choose the therapy with ^{131}I-MIBG or reject it. The physicians and the Medical Center will continue to offer their best care regardless of your choice.

Please ask all the questions that concern you about the treatment. Drs. Sisson, Beierwaltes, Shapiro and Hutchinson, and other physicians, will be pleased to answer your questions.

E. Consent to This Method of Treatment

I understand that the University will provide first-aid medical treatment in the unlikely event of physical injury resulting from research procedures. Additional medical treatment will be provided in accordance with the University's determination of its responsibility to do so. The University does not, however, provide compensation to a person who is injured while participating as a subject in research.

I have read the above information and am satisfied that I understand the value, nature and risks of receiving a radioactive drug for treatment of pheochromocytoma.

Patient's Name (Print)

Date

Signature

Witness

If signed for by Guardian, state relationship

THE UNIVERSITY OF MICHIGAN
Ann Arbor

August 2, 1984

RE: Radiopharmaceutical Treatment of Neuroblastoma

INVESTIGATOR: J. C. Sisson, M.D.

Approved with modification

The Committee to Review Grants for Clinical Research and Investigation Involving Human Beings of the University of Michigan Medical Center has met and considered the above named application.

The Committee is composed of fourteen members. Four members of associate professorial to professorial rank represent the Department of Internal Medicine. Four members of professorial rank represent the Departments of Surgery, Anesthesiology, Pediatrics and Obstetrics and Gynecology. Two members of associate professorial rank represent the Departments of Otorhinolaryngology and Psychiatry. Dr. Carl Cohen, Professor of Philosophy and Edward B. Goldman, Hospital attorney serve as representatives of a non-health related discipline. The Reverend Kenneth Phifer serves as the non-University affiliated member. Ann Munro serves as the non-science related representative.

Upon review of the above application the Committee has determined independently that the rights and welfare of the individuals involved in this research are carefully guarded. The methods used to obtain informed consent are appropriate. EACH INVESTIGATOR IS REQUIRED TO INFORM THE COMMITTEE OF ANY CHANGE IN RESEARCH PROTOCOL OR ANY UNANTICIPATED NEGATIVE CHANGE IN THE HEALTH OR BEHAVIOR OF A SUBJECT THAT MAY BE ATTRIBUTABLE TO THE RESEARCH AND TO REPORT THESE PROMPTLY TO THE COMMITTEE. The investigator agrees to retain in his files the written consent form signed by each participant. The investigator agrees to resubmit an application for continued approval of this investigation at intervals no greater than one year from the date of initiation of this research.

James C. Sisson

Investigator's signature

William W. Coon, M.D., Chairman

Approved provided investigator's phone number is added to consent form and patients are told they are free to refust to particip

Peter A. Ward, M.D., Acting Dean
University of Michigan Medical School

Alfred S. Sussman, Ph.D.
Vice President for Graduate Studies and Research
University of Michigan

Radioactive Drug Research Committee and
Subcommittee on Human Use of Radioisotopes

April 14, 1982

PRESENT: Carey, Froelich, Hicks, Sinsheimer, Solari and Bishop

At our last committee meeting we reviewed an application from Dr. Beierwalters to use 10mCi ^{123}I-MIBG for the diagnosis of extra adrenal pheochromocytomas (82-023). There were some criticisms concerning the informed consent in that protocol. We approved the application contingent on clarification of the informed consent. This clarification was accomplished through an exchange of memoranda with Dr. Beierwalters and the application was approved.

An application was received from Dr. Beierwalters to use ^{131}I-MIBG in high doses for the treatment of pheochromocytomas. Dr. Sisson is working with Dr. Beierwalters on this application (82-052). An IND application has been submitted for this use. The investigators plan to tailor the dose of the isotope in such a way that more than 2,000 rads will be delivered to each metastatic lesion. Mr. Carey had some questions concerning the estimation of dose. He noted that dose calculations would depend on a relatively accurate estimation of volume of the individual lesions. This could probably be accomplished reasonably well if tracer studies and calculations of dosimetry were accomplished before the treatment dose is given. Mr. Carey will discuss this matter with Dr. Sisson. Mr. Solari was questioned concerning the environmental hazzards involved in using this radio pharmaceutical in treatment doses. This would probably be handled much as the treatment doses of ^{131}I for thyroid disease. Mr. Solari saw no problem with this. It was reported by the chairman that Dr. Sisson had requested permission to treat a single patient with ^{131}I-MIBG on March 2. This approval was granted by the chairman with the understanding that approval would also be obtained from the FDA and this is recorded in the chairman's memorandum of March 9, 1982. A record of the approval of this project by the University of Michigan IRB was not identified. The chairman will look into this matter further and report back to the committee. It was moved by Carey second by Froelich that we approve this application. The motion carried 6-0.

An application was received from Dr. Beierwalters for the use of ^{123}I-Iodobenzene for the imaging of brain myelin. (82-078) It was noted that no informed consent form for volunteers was submitted with the protocol. There were two copies of the patient informed consent. It would appear that a separate and different informed consent form would need to be used for the volunteers in this project. Several of the committee members were concerned about possible toxicity of the iodobenzene and benzene derived from the apparent compound. It was thought that this application should be tabled until these two matters are clarified.

RADIOACTIVE DRUG RESEARCH COMMITTEE AND THE SUBCOMMITTEE ON THE HUMAN USE OF RADIOISOTOPES

September 12, 1984

PRESENT: Carey, LaDu, Riggs, Shapiro, Solari, and Bishop

Three requests have been received from Dr. Jeffrey Halter dated June 29, 1984. 84-044 involved the use of tritiated gluclose in the study of neural regulation of gluclose metabolism. 84-045 involved the use of tritiated epineiphine and 84-046 involved the use of tritiated norepineiphine. These later two studies are entitled "Aging and Autonomic Nervous System Function in Man". Although Dr. Halter supplied reprints and manuscripts concerning pervious work with these radionuclides, a specific protocol concerning future use of these materials was not supplied. Questions were raised about the significance of studies using the labeled methyl group in both the epineiphine and norepineiphine studies. A statement was included concerning the procedures for handling the radionuclide and preparing them for injection. However, there was no statement concerning quality control on these radiopharmaceuticals concerning sterility and pyrogenicity. The dosimetry calculations appeared to be entirely satisfactory. It was thought that we should have a statement concerning the absorbed radiation dose to specific organs. It should be recorded that because of the delay between the receipt of these applications and the meeting time of the Committee, and because the dosimetry estimates were within acceptable limits, the Chairman approved the application of the radionuclides in the study of two patients. It was the consensus of the Committee that these applications should not be approved at this time, and should be held until the forgoing described conditions have been met.

Dr. Sisson submitted a copy of his application to the Food and Drug Administration for modification of IND 17,239 for the therapeutic use of radioiodine meta-iodobenzylguanidine (MIBG). Dr. Sisson plans to use this in the treatment of patients with neuroblastoma. It was reported that the FDA had responded with some suggestions concerning the informed consent for this project and Dr. Sisson had answered their criticisms. There was some discussion concerning the environmental safety since there will be children treated with this material and because of the radioactivity in the urine of such children. These patients will be treated in the Clinical Research Center where the staff is familiar with the handling of radioactive waste. It was thought that the Radiation Control Service could make appropriate recommendations to the staff handling these patients. It was thought that the Committee should have copies of the letter from the FDA concerning Dr. Sisson's application and a copy of his response to that letter. With these considerations in mind, it was moved by Carey, seconded by Riggs that we approve this project. The motion carried 5-0 with Dr. Shapiro abstaining.

UNIVERSITY HOSPITAL

LOCATION DATE SERVICE

RADIOIODINE THERAPY PRESCRIPTION

Age [redacted] Sex [redacted]

Diagnosis Neuroblastoma

Reg. No. [redacted] Class

Name

Address

Number	Dose (in Millicuries)	Name	Date	Time
1	200 mCi	Prescribed by: Jr Sisson	9/16/85	1030
		Calibrated by:		
		Given by:		
		Prescribed by:		
		Calibrated by:		
		Given by:		
		Prescribed by:		
		Calibrated by:		
		Given by:		
		Prescribed by:		
		Calibrated by:		
		Given by:		
		Prescribed by:		
		Calibrated by:		
		Given by:		

CAUTION: Investigational Drug-Limited Use Only
CAUTION: RADIOACTIVE MATERIAL
NUCLEAR PHARMACY
U of M Hosp. Ann Arbor, Mi.
740 259 Dr. UMH NP
[redacted]
I-131NP-292 (mIBG)
NEUROBLASTOMA THERAPY
09-16-1985 14:53
200 mCi 30 ml

205347X

NUCLEAR MEDICINE [redacted]

Control 09128SNP292T99 Product ^{131}I NP.292 (mIBG Thea

Activity 222 mCi Volume 20.0 ml

Time 1445 CONCENTRATION 11.1 mCi/ml

CAUTION: Investigational Drug-Limited to Use Only

CAUTION RADIOACTIVE MATERIAL
NUCLEAR PHARMACY
U of M Hosp. Ann Arbor, Mi.
740 250 Dr. [redacted] NP
[redacted]
I-131NP-292 (mIBG)
NEUROBLASTOMA THERAPY
09-16-1985 14:53
200 mCi 30 ml

Date: 9/16/85 Time:	Date: Time:	
Name: Sterility + Pyrogen testing	Name:	
Dose: Vol:	Dose: Vol:	
Activity Dispensed 203 mCi	Activity Dispensed J Burke	Activity Dispensed
Date: Time:	Date: Time:	Date: Time:
Name:	Name:	Name:
Dose: Vol:	Dose: Vol:	Dose: Vol:
Activity Dispensed	Activity Dispensed	Activity Dispensed
Date: Time:	Date: Time:	Date: Time:
Name:	Name:	Name:
Dose: Vol:	Dose: Vol:	Dose: Vol:
Activity Dispensed	Activity Dispensed	Activity Dispensed
Date: Time:	Date: Time:	Time:
Name:	Name:	Name:
Dose: Vol:	Dose: Vol:	Dose: Vol:
Activity Dispensed	Activity Dispensed	Activity Dispensed
Date: Time:	Date: Time:	DECAYED TO WASTE
Name:	Name:	DATE: 9/16/85
Dose: Vol:	Dose: Vol:	INITIALS:
Activity Dispensed	Activity Dispensed	Activity Dispensed

UNIVERSITY HOSPITAL

LOCATION DATE SERVICE

RADIOIODINE THERAPY PRESCRIPTION

Age [redacted] Sex [redacted]

Diagnosis ... Neuroblastoma

Req No [redacted] Class

Address

Number	Dose (in Millicuries)	Name	Date	Time
2	200mCi	Prescribed by: B. Shapiro	1/14/86	9:30 am
		Calibrated by: Hal A. Paxton	1/14/86	1655
		Given by: B. Shapiro	1/14/86	
		CAUTION: RADIOACTIVE MATERIAL NUCLEAR PHARMACY U of M Hosp. Ann Arbor, Mi. [redacted] I-131NaI-892 (mCi) SPECIAL THERAPY STUDY 01-16-1986 14:58 200 mCi 14.92 mCi CAUTION: Investigational Drug-Limited Use Only		
		Prescribed by:		
		Calibrated by:		
		Given by:		
		Prescribed by:		
		Calibrated by:		
		Given by:		
		Prescribed by:		
		Calibrated by:		
		Given by:		

205347X

NUCLEAR MEDICINE UNIT

AUD. ___ ___ ___

Control 0118GMP292T104 Product ^{131}I-NP292 THERAPY

Activity 268 mCi Volume 20 ml

Time 1640 CONCENTRATION 13.4 mCi/ml

CAUTION: Investigational Drug-Limited Use Only

CANCER RESEARCH CENTERS
NUCLEAR PHARMACY
U of M Hosp. Ann Arbor, MI
[redacted]

I-131MP-292 (mIBB)
SPECIAL THERAPY STUDY
01-14-1986 16:50
200 mCi 14.92 ml

Activity Dispensed 216mCi JH

Date: 1/15/86 Time:	Date: Time:	Date: Time:
Name: Sterility + Pyrogen testing	Name:	Name:
Dose: Vol: 1.3 ml.	Dose: Vol:	Dose: Vol:
Activity Dispensed JJ Burke	Activity Dispensed	Activity Dispensed
Date: Time:	Date: Time:	Date: Time:
Name:	Name:	Name:
Dose: Vol:	Dose: Vol:	Dose: Vol:
Activity Dispensed	Activity Dispensed	Activity Dispensed
Date: Time:	Date: Time:	Date: Time:
Name:	Name:	Name:
Dose: Vol:	Dose: Vol:	Dose: Vol:
Activity Dispensed	Activity Dispensed	Activity Dispensed
Date: Time:	Date: Time:	Date: Time:
Name:	Name:	Name:
Dose: Vol:	Dose: Vol:	Dose: Vol:
Activity Dispensed	Activity Dispensed	Activity Dispensed
Date: Time:	Date: Time:	DECAYED TO WASTE
Name:	Name:	DATE: 1/15/86
Dose: Vol:	Dose: Vol:	INITIALS: JH
Activity Dispensed	Activity Dispensed	Activity Dispensed

UNIVERSITY HOSPITAL

RADIOIODINE THERAPY PRESCRIPTION

LOCATION | DATE | SERVICE

Reg. No. [redacted] Class

Name [redacted]

Address

Age [redacted] Sex [redacted]

Diagnosis Neuroblastoma

Number	Dose (In Millicuries)	Name	Date	Time
3	200 mCi ^{131}I-mIBG	Prescribed by: B. Shapiro	2/25/86	9:00
		Calibrated by:		
		Given by: B. Shapiro	2/25/86	
		Prescribed by:		
		Calibrated by:		
		Given by:		
		Prescribed by:		
		Calibrated by:		
		Given by:		
		Prescribed by:		
		Calibrated by:		
		Given by:		
		Prescribed by:		
		Calibrated by:		
		Given by:		

CAUTION: Investigational Drug-Limited Use Only

CAUTION: RADIOACTIVE MATERIAL
NUCLEAR PHARMACY
U of M Hosp. Ann Arbor, MI.
740 56 Dr. UMHA lw
[redacted]
I-131NP-292 (mIBG)
SPECIAL THERAPY STUDY
02-25-1986 13:37
200 mCi 14.18 ml

205347X

NUCLEAR MEDICINE UNIT

Control: 022486NP292T1N2 Product: 131 I-NP 292 Therapy

Activity: 282 mCi Volume: 20 ml

Time: 1315 Concentration: 14.1 mCi/ml

CAUTION: Investigational Drug-Limited Use Only

CAUTION: RADIOACTIVE MATERIAL
NUCLEAR PHARMACY
U of M Hosp. Ann Arbor, Mi.
740 56 Dr. UMH. 1w
[redacted]
I-131NP-292 (mIBG)
SPECIAL THERAPY STUDY
02-25-1986 13:38
200 mCi 14.18 ml

Activity Dispensed: 220 ✓

Date: 2/25/86 Time:	Date: Time:	
Name: Sterility + Pyrogen Testing	Name:	
Dose: Vol: 1.3 ml.	Dose: Vol:	
Activity Dispensed: J. Burke	Activity Dispensed:	
Date: Time:	Date: Time:	Date: Time:
Name:	Name:	Name:
Dose: Vol:	Dose: Vol:	Dose: Vol:
Activity Dispensed:	Activity Dispensed:	Activity Dispensed:
Date: Time:	Date: Time:	Date: Time:
Name:	Name:	Name:
Dose: Vol:	Dose: Vol:	Dose: Vol:
Activity Dispensed:	Activity Dispensed:	Activity Dispensed:
Date: Time:	Date: Time:	Date: Time:
Name:	Name:	Name:
Dose: Vol:	Dose: Vol:	Dose: Vol:
Activity Dispensed:	Activity Dispensed:	Activity Dispensed:
Date: Time:	Date: Time:	DECAYED TO WASTE
Name:	Name:	DATE: 2/25/86
Dose: Vol:	Dose: Vol:	INITIALS: MM
Activity Dispensed:	Activity Dispensed:	Activity Dispensed: