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Compassionate Use of ^{131}I -MIBG for Patients with Malignant Pheochromocytoma

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**^{131}I -METAIODOBENZYLGUANIDINE (^{131}I -MIBG) THERAPY FOR PATIENTS WITH
MALIGNANT PHEOCHROMOCYTOMA & RELATED TUMORS**

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A Best Available Therapy / Compassionate Use Protocol

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1.0 SPECIFIC AIMS

Malignant adrenal pheochromocytoma (PHEO) and extra-adrenal pheochromocytoma (paraganglioma, PGL) remain fatal cancers for the majority of patients, with an average survival of 4.5 years. ^{131}I -metaiodobenzylguanidine (^{131}I -MIBG) is a norepinephrine analog that concentrates in adrenergic tissue and therefore holds promise for cell-specific treatment of malignant PHEO/PGL. ^{131}I -MIBG is active against malignant PHEO/PGL. The associated hematopoietic toxicity can be abrogated with autologous stem cell rescue. ^{131}I -MIBG given in doses of 8-12 mCi/kg with stem cell rescue, if necessary, is a reasonably safe and effective palliative therapy for patients with refractory or relapsed malignant PHEO/PGL.

Primary Aims:

- Provide palliative therapy for patients with malignant PHEO/PGL.
- Gain more information about acute and late toxicity of ^{131}I -MIBG therapy for patients who have metastatic PHEO/PGL.

Secondary Aim:

- Obtain disease and symptom responses on patients with malignant PHEO/PGL who are not eligible for other therapy of higher priority.

2.0 BACKGROUND AND RATIONALE

Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare tumors, with an incidence of 2-8 cases per million annually. These tumors develop in both children and adults. About 15-20% metastasize. Chemotherapy for this tumor usually consists of a combination of cyclophosphamide, vincristine, and dacarbazine delivered over two days and repeated every 3 weeks. Such combined chemotherapy is ineffective for the majority of patients with metastatic PHEO/PGL. A few patients with malignant PHEO have experienced remissions with sunitinib, but the drug may produce severe toxicity and the experience with that drug is limited. Those patients who do experience a remission with chemotherapy must continue it indefinitely to stay in remission. However, most such patients experience such severe side effects from the chemotherapy (marrow suppression, neuropathy, etc) that their chemotherapy must be discontinued. Thus, chemotherapy is either ineffective or intolerable for the vast majority of patients with metastatic PHEO/PGL.

2.1 Previous Human Experience with ^{131}I -MIBG

Meta-iodobenzylguanidine (MIBG) is a guanethidine derivative structurally resembling norepinephrine. Originally synthesized by Short and Darby as a potential antihypertensive agent [1], MIBG was investigated by Wieland and his colleagues at the University of Michigan as a potential radiolabeled adrenergic neuron imaging agent [2]. MIBG was shown to have marked affinity for, and concentration in, the adrenal medulla, where it is subsequently stored in

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neurosecretory granules [3-5].

MIBG can be labeled with radioactive isotopes of iodine, suitable for diagnostic imaging applications (^{123}I), or for both imaging and therapy (^{131}I). MIBG has been extremely useful for the scintigraphic localization of pheochromocytomas and for the characterization of incidentally discovered adrenal masses [6-8]. MIBG has also been shown to concentrate in several neoplasms of neuroectodermal origin, particularly PHEO/PGL and neuroblastoma. Diagnostic MIBG scintigraphy is currently used routinely for PHEO/PGL disease staging and response evaluation [2,9-12].

^{131}I -MIBG has undergone extensive single institution, and more recently, cooperative clinical trials for the treatment of malignant pheochromocytoma and neuroblastoma [13-19]. This includes trials at UCSF, Children's Hospital of Philadelphia, and University of Michigan, as well as in the NANT consortium. The results from these trials show that MIBG is active against refractory neuroblastoma with a response rate of 30-40% and is highly effective therapy for disease palliation [13,14,15,17,20,21,22,23,24]. Non-hematologic toxicity, even at substantial doses of MIBG, has usually been minimal and included brief nausea and vomiting, mild reversible myelosuppression, transient hepatic dysfunction, adrenal insufficiency (in one patient), and chemical hypothyroidism. The most significant toxicity has been prolonged thrombocytopenia, most marked in patients with tumor in the bone marrow, and more transient neutropenia. Thus, ^{131}I -MIBG appears to be a highly specific and active agent for treatment of human neuroblastoma and PHEO/PGL, but the optimal method for delivering this novel therapy remains to be determined.

2.2 UCSF Experience

Fifty-five patients with metastatic PHEO/PGL have been treated with doses of ^{131}I -MIBG ranging from 492 mCi to 1160 mCi. Prior publications have described our first 12 patients and first 30 patients. We now have response data from the first 50 patients with metastatic PHEO/PGL treated at UCSF with ^{131}I -MIBG:

Cumulative ^{131}I -MIBG ranged from 492-3191 mCi. Autologous hematopoietic stem cells were collected and cryopreserved prior to treatments with ^{131}I -MIBG in doses >12 mCi/kg or >500 mCi/kg. Thirty-five patients were treated once, while 15 patients received two or three treatments. By RECIST criteria, the overall combined complete response (CR) plus partial response (PR) rate was 22%. Additionally, 35% of patients achieved a CR or PR response in at least one measure of hormonal response, without any progressive disease, and an additional 8% of patients maintained stable disease >12 months. Thirty-five percent of patients experienced progressive disease within one year following therapy. The estimated 5-year overall survival was 64%. Toxicities included: grade 3-4 neutropenia (87%) and thrombocytopenia (83%).

Grade 3-4 non-hematologic toxicity included: pulmonary embolism (n=1), fever with neutropenia (n=7), acute hypertension (n=10), infection (n=2), hypogonadism (n=6).

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Two patients developed bronchiolitis obliterans organizing pneumonia (BOOP) after ¹³¹I-MIBG doses of 845 mCi (8.1 mCi/kg) and 1062 mCi (16.9 mCi/kg) respectively; both patients recovered. Two patients developed acute respiratory distress syndrome (ARDS) after ¹³¹I-MIBG doses of 1,160 mCi (18 mCi/kg) and 1,030 mCi (12.1 mCi/kg) respectively. One patient (with a heavy secretory tumor burden and severe nephrotic syndrome) died from ARDS. Two patients developed myelodysplastic syndrome (MDS) with acute myelogenous leukemia after partial remissions lasting 5 and 2 years following ¹³¹I-MIBG at cumulative doses of 1,712 mCi and 1832 mCi respectively.

3.0 SUBJECT RECRUITMENT AND SELECTION

This is a best available therapy/compassionate use study designed to determine the palliative benefit and toxicity of ¹³¹I-MIBG in patients with progressive pheochromocytoma (PHEO) or paraganglioma (PGL) who are not eligible for therapies of higher priority. Patients may receive a range of doses depending on stem cell availability and tumor involvement of bone marrow. Response rate, toxicity, and time to progression and death will be evaluated. All eligible patients will be offered participation in this study regardless of gender or race.

3.1 Eligibility criteria

3.11 Diagnosis: Refractory or relapsed PHEO/PGL with original diagnosis based on tumor histopathology or the finding of PHEO/PGL tumor cells in the bone marrow. The diagnosis may also be based upon the presence of high plasma fractionated metanephrines or high urine catecholamines/metanephrines with diagnostic MIBG uptake.

3.12 Age: > 2 years and able to cooperate with radiation safety restrictions during therapy period.

3.13 Disease status: It must be determined that either the PHEO/PGL tumors are not amenable to safe surgical resection or are metastatic. Disease evaluable by MIBG scan must be present within 6 weeks of study entry and subsequent to any intervening therapy.

3.14 Life Expectancy: greater than 3 months.

3.15 Lanksy and Karnofsky Performance Status: 70% or higher.

3.16 Stem cells: Patients must have an autologous hematopoietic stem cell product available for re-infusion after MIBG treatment at doses of >12 mCi/kg *or* >500 mCi (whichever is smaller) if needed. The minimum quantity for purged or unpurged peripheral blood stem cells is 1.0×10^6 CD34+ cells/kg (optimum $\geq 2 \times 10^6$ CD34+ cells/kg). The minimum dose for bone marrow is 1.0×10^8 mononuclear cells/kg (optimum $> 2.0 \times 10^8$ mononuclear cells/kg). If no stem cells are available, then the dose of ¹³¹I-MIBG should

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be ≤ 12 mCi/kg *and* ≤ 500 mCi. (Note: Due to the nature of radioisotope decay, the administered dose limitations may have an inherent tolerable variability of ± 1.2 mCi/kg *or* ± 50 mCi.)

3.17 Prior Therapy: Patients may enter this study with or without having had other therapy for recurrent tumor. Patients may be treated who have not had chemotherapy or radiation therapy. Patients may also be treated who have failed to respond to standard chemotherapy or radiation therapy. Patients must have fully recovered from the toxic effects of any prior therapy. At least 2 weeks should have elapsed since any anti-tumor therapy and the patient must meet hematologic criteria below. Three months should have elapsed in the case of completing radiation to any of the following fields: total craniospinal, total abdominal, whole lung, total body irradiation). Cytokine therapy (eg G-CSF, GM-CSF, IL-6, erythropoietin) must be discontinued a minimum of 24 hours prior to MIBG therapy. Prior ^{131}I -MIBG therapy is allowed if > 3 months previous and if the patient has adequate hematopoietic stem cells available for planned doses of >12 mCi/kg *or* >500 mCi. Cumulative lifetime dose of ^{131}I -MIBG, including the planned treatment, should not exceed 36 mCi/kg.

3.18 Organ Function

3.181 Liver function: bilirubin $< 2x$ upper limit of normal (ULN). Exception: Gilbert syndrome); AST $\leq 10x$ ULN.

3.182 Kidney function: Creatinine $\leq 2x$ ULN.

3.183 Hematopoietic Criteria: Patients must have adequate hematopoietic function (without transfusion): ANC $\geq 750/\mu\text{L}$; Platelets $\geq 50,000/\mu\text{L}$ if stem cells are not available; if stem cells are available, the patient should be independent of platelet transfusions with a platelet count of at least $20,000/\mu\text{L}$. Hemoglobin $\geq 10\text{g/dl}$ at time of treatment (transfusion allowed). Patients with granulocytopenia and/or thrombocytopenia due to tumor metastatic to the bone marrow may be eligible after discussion with Dr. Fitzgerald or designee.

3.184 Normal lung function as manifested by no dyspnea at rest or exercise intolerance, no oxygen requirement.

3.185 No clinically significant cardiac dysfunction, normal EKG and EJ $>50\%$

3.186 Signed informed consent: The patient and/or the patient's legally authorized guardian must acknowledge in writing that consent to become a study subject has been obtained, in accordance with institutional policies approved by the U.S. Department of Health and Human Services.

3.2 Exclusion criteria

- 3.21 Patients with disease of any major organ system that would compromise their ability to withstand therapy. Any significant organ impairment should be discussed with the Study Chair or Vice Chair prior to patient entry.
- 3.22 Because of the teratogenic potential of the study medications, no patients who are pregnant or breast feeding will be allowed. Patients of childbearing potential must practice an effective method of birth control while participating on this study, to avoid possible pregnancy.
- 3.23 Patients who are on hemodialysis.
- 3.24 Patients with active infections that meet grade 3-4 toxicity criteria.
- 3.2 **Registration procedure:** Call Fabienne Hollinger (415) 514-0238 or Dr. Fitzgerald (415) 665-1136 prior to treatment and fax a copy of the consent form to Dr. Fitzgerald (415) 665-8500.

4.0 TREATMENT

- 4.1 **On Study:** Disease status and pre-therapy organ evaluation will be done as detailed in Section 5.0. Each patient will undergo a diagnostic quality ¹³¹I- or ¹²³I-MIBG scan within 6 weeks of entry onto study and without other intervening anti-tumor therapy. See Section 5.0 Required Observations.

4.2 Treatment

- 4.21 ¹³¹I-MIBG Therapeutic Administration. Therapeutic ¹³¹I-MIBG will be synthesized at Nuclear Diagnostic Products (NDP; Rockaway, New Jersey) with specific activities of 9-18 Ci/mmol. The therapeutic dose: 8-12 mCi/kg (maximum 800 mCi ± 10% at investigator's discretion; any dose > 500 mCi ± 10% requires stored stem cells) will be diluted in 25 ml of normal saline, and will be infused intravenously through a patient's peripheral or central line over 120 minutes. The patient will remain in a radiation protected isolation room until radiation emissions are ≤ 2 mr/hr at a 1 meter distance or meets institutional and state guidelines. This usually takes 4-6 days. In all cases, special shielding will be equipped in the room to minimize exposure to the outside environment and personnel will observe institutional radiation safety precautions.
- 4.22 Bladder protection. It is recommended that a urinary catheter be inserted prior to the MIBG infusion and retained for a minimum of 72 hours or until the patient is released from radiation isolation if incontinent. The catheter will prevent accumulations of large amounts of radioactivity in the bladder. Drainage of urine will be into a continuously

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running toilet or into a sterile bag housed in lead shielding; the bag will be emptied every 3-12 hours depending on the size of the patient and the rate of urine output. Intravenous fluids will be administered at 75-125 ml/m²/hour to help maintain urine flow and isotope excretion for at least 72 hours. In case the patient is unable to cooperate with this catheter and the isolation, sedation and temporary placement of a spica body cast may be necessary.

4.23 Thyroid protection. For the therapeutic MIBG administration, KI solution will be administered in a loading dose of 6 mg/kg p.o. the night before the MIBG injection, then 1 mg/kg/dose q 4h days 0-7, then 1 mg/kg/day through day 45 post injection. Potassium perchlorate will be given as an additional blocking agent, beginning with 8 mg/kg loading dose on the evening before the MIBG injection, then 2 mg/kg, p.o., q 6h for 5 days following the MIBG. The doses may be reduced in the event of gastrointestinal intolerance.

4.24 Imaging. For all patients, a scintigraphic MIBG imaging study, comparable to the diagnostic scan, will be done near the time of discharge, usually on day 4 or 5 post-treatment. This scan is performed to confirm tumor uptake and also to survey for occult sites of disease. Patients will not receive any MIBG injection for this scan. Some patients may elect to participate in a separate organ or tumor dosimetry study, which would require a separate consent and extra images.

4.25 G-CSF. Patients whose ANC is less than 500/uL after MIBG infusion will begin G-CSF 5 mcg/kg/day (or an equivalent single dose of Neulasta) subcutaneously until neutrophil recovery.

4.3 Post-Treatment Evaluation

Post-treatment evaluation will be performed 8-12 weeks after treatment. Required studies are detailed in Section 5.0

4.31 Toxicity. Complete FDA Form 3500A (Medwatch) for grade 3 and 4 toxicities except expected hematologic toxicities and fever. Deaths occurring <6 weeks post treatment should be reported.

4.4 Criteria for hematopoietic stem cell infusion.

It is recommended that a patient receive an infusion of a portion of their cryopreserved autologous hematopoietic stem cells if they develop grade 4 hematologic toxicity following ^{131}I -MIBG therapy and continue to have an ANC < 200/uL on G-CSF/Neulasta without signs of recovery for > 2 weeks. In addition, any patient requiring platelet transfusions more than two times weekly for 2 consecutive weeks will receive hematopoietic stem cell rescue. Stem cell infusion may occur sooner or later if indicated (i.e. due to an infectious or bleeding complication) after consultation with the Study Chair or designee.

4.5 Criteria for subsequent treatment. Patients may be eligible for additional ^{131}I -MIBG therapies if they meet the following criteria:

- 4.51** Minimum of eight weeks from previous MIBG therapy on this study.
- 4.52** Response or stable disease after the first infusion. If patient responds with a CR to the first infusion, the patient may receive a second therapy as consolidation.
- 4.52** Meets all other criteria as outlined in eligibility and pre-treatment evaluation sections above except for platelet count. Patient may be thrombocytopenic, but requiring no more than 1 platelet transfusion per week to maintain counts above 20,000.
- 4.53** To receive a subsequent course at > 12 mCi/kg or > 500 mCi (± 10%), a patient must have cryopreserved hematopoietic stem cells available in sufficient quantity, as stated in 3.14.

5.0 REQUIRED OBSERVATIONS

Required observations listed are for toxicity and response monitoring. More frequent or additional tests should be ordered as clinically indicated.

Observation	Before or at Entry	Day 0-7 ¹	Day 7-56	Day 56-120
Physical Exam	X			X
CBC with Diff, Platelet count	X		Weekly ²	X
Urinalysis	X			X
AST, ALT, T. Bilirubin, Albumin	X		Weekly	X
BUN, creatinine	X		Weekly	X
Electrolytes	X			X
Ca, Mg, Phos	X			X
FT ₄ , TSH	X			X
Serum β-HCG ³	X			
Bilat BM Asp/Bx	X			X ⁵
Tumor Imaging (CT or MR) ⁴	X			X
¹³¹ I-MIBG Infusion		Day 0		
MIBG Diagnostic Scan (REQUIRED)	X			X
MIBG whole body scan		Between D 3-7		
Urine fractionated catecholamines & metanephrines and	X ⁴			X

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serum chromogranin A				
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1. No routine bloodwork or radiologic studies are required while patient is hospitalized in radiation protected environment unless clinically indicated. Patients with prior electrolyte imbalance should be monitored during the hydration.
2. Twice weekly CBC/Diff/Plt until ANC >500/mm³ & Plt count > 20,000 x 3 days without transfusion.
3. Obtain for females 10 years of age and older or post-pubertal.
4. Tumor imaging = CT/MRI as needed for optimum visualization of all areas of bulk tumor (primary & metastasis). Must be performed ≤ 6 weeks prior to study entry. Repeat urine fractionated catecholamines & metanephrines and serum chromogranin A only if elevated pre-therapy. If the patient receives further therapy on other protocols at ANY TIME POINT, no further tumor studies will be subsequently required for this protocol.
5. BM aspirate/biopsy must be repeated only if positive at study entry

5.1. Recommended follow up observations:

CBC with differential and platelet count, ALT, AST, bilirubin, T₄, TSH and MIBG scan every 3 months until 1 year post treatment, then q 6 months until progression, death or other therapy. Other disease evaluation as clinically indicated.

6.0 RESPONSE CRITERIA

All patients who are registered will be accounted for in the report of the results. Patients who complete one course of therapy will be evaluated for response at 2-4 months post treatment, or earlier if proceeding to other therapy. Volumetric measurable disease will be assessed with the same modality (MRI or CT scan) as was performed at the on study evaluation. The following disease status definitions will be used.

RECIST RESPONSE CRITERIA used for measurable soft tissue tumor

Overall response:

Response	Primary Tumor*	Metastatic Sites*#
CR	No Tumor	No tumor; catecholamines, metanephrines and chromogranin A all normal.
PR	Decreased >50%	All measurable sites decrease by > 50%. Bones and bone marrow: number of positive bone sites decreased by >50%; bone marrow tumor decreased by 50%

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MR	No new lesions; >50% reduction of any measurable lesion (primary or metastases) with <50% reduction in any other; <25% increase in any existing lesion.
NR	No new lesions; <50% reduction but <25% increase in any existing lesion.
PD	Any new lesion; increase of any measurable lesion by >25%; previous negative marrow positive for tumor.

*Evaluation of primary and metastatic disease as outlined.

#One positive marrow aspirate or biopsy allowed for PR if this represents a decrease from the number of positive sites at diagnosis.

7.0 STATISTICAL CONSIDERATIONS

Efficacy

This is a compassionate use protocol to be used as best available therapy for palliation in patients who are not eligible for protocols of higher priority. The endpoints to be analyzed will be progression free survival, survival, response and toxicity. The anticipated accrual is 4 patients per year with a total accrual of approximately 50 patients.

Toxicity

Because this is a group of patients with very far advanced disease, stopping rules will be in place. If there is >1 toxic death in the first 10 patients treated, or >2 in the first 20, then the protocol will be suspended and the data reviewed. All grade 3 and 4 toxicities will be recorded and reviewed every six months. If non-hematologic grade 4 toxicity is seen in >15% of patients, the protocol will be suspended and reviewed.

Sample Size Justification and Accrual

This study will provide additional safety data for FDA approval of MIBG and efficacy data. The FDA is interested in long-term safety and toxicity data, so the accrual of additional patients beyond that of the previous phase II study will allow this goal to be met. It is anticipated that ¹³¹I-MIBG will eventually be approved for commercial use in patients with metastatic pheochromocytoma and paraganglioma, and therefore prolongation of this compassionate use protocol will no longer be necessary.

Safety Analysis

Grade 3 and 4 adverse events will be coded by the NCI Common Toxicity Criteria v3 and summarized. Within each body system, the severity will be summarized, as well as worst toxicity overall for each patient.

8.0 FINANCIAL CONSIDERATIONS

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Research subjects will not be paid for participation in this study. The cost of the MIBG and hospital stay will be covered by 3rd party payers. ^{131}I -MIBG has been approved by the FDA for cost recovery. Stem cell harvest and infusion, outpatient visits, supportive care, MIBG scintigraphy and routine scans and laboratory monitoring will be billed in the usual manner, i.e. to third party payers.

9.0 POTENTIAL RISKS

^{131}I -METAIODOBENZYLGUANIDINE (^{131}I -MIBG)

Likely (happens to 21-100 patients out every 100 patients)	Less Likely (happens to 5-20 patients out every 100 patients)	Rare (happens to < 5 patients out every 100 patients)
<ul style="list-style-type: none">• Decrease in the number of red and white blood cells and platelets made in the bone marrow. You may need blood and platelet transfusions and usually stem cell infusions are necessary. The dose of ^{131}I-MIBG infusion used in this study may lower your blood counts.• Lowering the number of red blood cells, which may make you tired or pale• Nausea• Dry mouth• Alopecia (hair loss)• High or low blood pressure during ^{131}I-MIBG infusion• Loss of appetite	<ul style="list-style-type: none">• Fever or infection as a result of the low white blood cells. The infection may become serious.• Fatigue from low red blood cells• Not being able to get pregnant or have a child• Decreased function of the thyroid gland. This causes tiredness (fatigue), weight gain, constipation, and lower blood pressure. Treatment for life with a medicine to supplement the thyroid gland (you.e. Synthroid or related thyroid supplement) may be needed.• Respiratory or breathing problems	<ul style="list-style-type: none">• Pain and swelling in salivary glands• Urinary tract infection from having a urinary catheter placed. (This is a risk from having a urinary catheter placed for the ^{131}I-MIBG treatment not from the ^{131}I-MIBG itself.)• Bruising or bleeding from the low platelet count. Bleeding can rarely become serious.• Decreased function of adrenal gland. This affects your activity level and growth. It causes tiredness (fatigue), weight changes and blood pressure changes. You may need to take medicine to supplement the adrenal gland.• Decreased heart function• Irritation of the liver and/or kidneys. Because some of the radioactive ^{131}I-MIBG is taken up by the liver and kidneys, there is a possible risk of future liver and/or kidney damage from the ^{131}I-MIBG alone.• Second cancer, different from the kind of cancer you have now (leukemia).• Complications related to taking ^{131}I-MIBG may result in death• Dehydration• Pain at tumor site• Autonomic Neuropathy• Blood Clots

POTASSIUM IODIDE (KI, SSKI)

Likely (happens to 21-100 patients out of every 100 patients)	Less Likely (happens to 5-20 patients out of every 100 patients)	Rare (happens to <5 patients out of every 100 patients)
	<ul style="list-style-type: none"> • Gastrointestinal distress (nausea / vomiting / diarrhea / stomach pain) 	<ul style="list-style-type: none"> • Pain, tingling or weakness in arms and legs • Vasculitis • Flare-up of adolescent acne • Irregular heartbeat • Confusion • Tiredness • Fever • Hypersensitivity (rash, hives) • Burning of mouth / throat • Metallic taste • Rash • Hypothyroidism • Hyperthyroidism • Swelling of lymph glands

POTASSIUM PERCHLORATE (KCLO4)

Likely (happens to 21-100 patients out of every 100 patients)	Less Likely (happens to 5-20 patients out of every 100 patients)	Rare (happens to <5 patients out of every 100 patients)
	<ul style="list-style-type: none"> • Gastrointestinal distress (nausea / vomiting / diarrhea / stomach pain) 	<ul style="list-style-type: none"> • Unable to make red and white blood cells, platelets • Hypersensitivity (rash, hives)

In general, MIBG therapy has been well-tolerated by patients with pheochromocytoma and paraganglioma, many of whom have been heavily pretreated. The major risk for patients participating in this study is hematologic toxicity. The dose of MIBG chosen is expected to induce grade 4 hematopoietic toxicity in most patients. Thus, bleeding and/or infectious complications are possible and may be life threatening. Assuring hematopoietic stem cell availability, which may be used for hematopoietic “rescue,” or administering the lower doses of ¹³¹I-MIBG when stem cells are not available, minimizes these risks. The risk of hypothyroidism is minimized by administration of a blocking agent during and for 6 weeks following MIBG therapy. There is a very small risk of radiation exposure to family members. Nausea, hypertension or hypotension are sometimes observed during ¹³¹I-MIBG infusion, but respond readily to treatment. Secondary leukemia or other malignancy is also a known but rare (<5%) risk of radiation, particularly in patients who have also received extensive prior

therapy. There is a theoretical risk from the radiation exposure to organs in which the ¹³¹I-MIBG concentrates, such as bladder, gonads, heart, lungs, and liver. The use of the Foley catheter effectively decreases the residence time of the radioactivity in the bladder to less than 5 minutes, thereby decreasing the bladder exposure to less than 300 cGy. There is still some controversy about the exposure to the liver and heart, areas of concentration of ¹³¹I-MIBG, but, to date, grade 3 or 4 hepatotoxicity has been <7% and cardiac and renal toxicity have not been reported. Lastly, patients with refractory malignant pheochromocytoma and paraganglioma may develop unexpected complications that may be life threatening.

10.0 POTENTIAL BENEFITS

It is possible that this therapy may relieve pain and/or decrease tumor burden. This may increase survival duration and potentially allow for additional MIBG or other experimental therapies. It is unlikely that MIBG therapy alone will cure any patient with refractory pheochromocytoma or paraganglioma. Successful completion of this clinical trial may benefit future patients with malignant pheochromocytoma or paraganglioma.

11.0 RISK/BENEFIT ANALYSIS

Patients who will be entering this trial will have a limited life expectancy. Based upon phase II and pilot data, this research study appears to have a reasonable chance of directly benefiting the research subject with a minimum of non-hematopoietic toxicity and average hospital days of fewer than 7. Thus, the potential benefits outweigh the potential risks.

12.0 PROTECTION OF SUBJECTS

Study generated data will be maintained in locked offices or computers with access available only to those individuals directly involved with this study. A generated subject number will identify research subjects. All efforts will be undertaken to ensure patient confidentiality.

13.0 CONSENT/ASSENT

The physicians participating in this study will obtain written informed consent from the adolescent/adult patients and parents/legal guardians after providing a review of the study and the required procedures. Whenever possible, assent will be obtained from children between the ages of 7 and 12 and documented by means of the child's and the physician's signature on the consent form.

14.0 ADVERSE EVENT REPORTING AND DATA SAFETY MONITORING

14.1 Adverse Event Reporting

All patients will have toxicity monitoring for 6-8 weeks following ¹³¹I-MIBG therapy. Toxicities will be graded according to the Common Toxicity Criteria (CTC) version 3.0 (<http://ctep.info.nih.gov>) and attribution assigned. Toxicities will be summarized and reported annually to the FDA.

All toxicities will be categorized as either expected or unexpected. For the purposes of this trial, all unexpected Grade 4 toxicities and all deaths that occur in the first six weeks following treatment will be categorized as a Serious Adverse Event and will require expedited reporting. All toxic deaths will be reported by phone within 24 hours to the data center at UCSF and the FDA. MedWatch forms will be filed for all unexpected Grade 4 toxicities and deaths with each participating institution's IRB and the FDA. Unexpected Grade 4 toxicities and treatment-related deaths will also be reported in an expedited fashion for patients who remain in "treatment phase" after six weeks (i.e. no additional therapy). However, deaths due to progressive disease will not require expedited reporting after 6 weeks.

Other serious adverse events that are coded as unexpected Grade 2 and 3 toxicities will also be reported in expedited fashion as above. No Grade 1 toxicities will require expedited reporting.

All toxicities will be collected and summarized annually in reports to the IRB and FDA.

Grade 4 blood/bone marrow toxicities are EXPECTED and will not require expedited reporting. In addition, because Grade 3 febrile neutropenia is common, hospitalization for fever and neutropenia will be recorded but will not require expedited reporting. Grade 4 febrile neutropenia (septic shock) or any Grade 4 infection will be reported using the expedited system noted above.

Grade 4 pain due to the patients disease and/or hospitalizations to manage symptoms from the underlying disease will be recorded but not require expedited reporting.

14.1.1 Persistent Adverse Events

An adverse event that persists from one course (cycle) to another should be reported only once unless the grade becomes more severe in a subsequent course. An adverse event, which resolves and then reoccurs during a different course (cycle) must be reported each course (cycle) it re-occurs.

14.1.2 Baseline Adverse Events

An adverse event should NOT be reported if a patient is entered on a study with a pre-existing condition (e.g., elevated laboratory value). If the adverse event increases in severity, the investigator should re-assess the event to determine if the event should be reported. No

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modification in grading should be made to account for abnormalities noted at baseline.

14.2 Data Safety Monitoring Plan

This protocol has been submitted to the FDA and the UCSF Comprehensive Cancer Center Protocol Review Committee and the Pediatric Clinical Research Center at UCSF. The study accrual and toxicity and any deaths will be reviewed every six months by the study chair, Dr. Fitzgerald, along with the nurse coordinator and the statistician. Requirements for the INDs will be strictly adhered to by expedited and annual reports to the FDA.

If more than one unexpected or not-previously-described SAE attributable to study drug is observed, accrual to the protocol will be suspended. An ad hoc committee comprising the study chair (Dr. Fitzgerald), other lead investigators, and at least one subspecialist not participating in the trial will be convened by the study chair. An assessment of the risks to patients will be made, and a recommendation to continue with the study or close the trial will be made to the IRB for review. Should a decision be made to continue with the trial, the modifications to the protocol, the updated assessment of risks and benefits, and a modified informed consent will be submitted to the IRB prior to reopening the trial.

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Appendix 1: ^{131}I -MIBG Drug Information

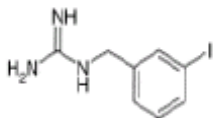
1. Description

Chemical name: ^{131}I -meta-iodobenzylguanidine

CAS RN: (for un-iodinated MIBG): 80663-95-2

Laboratory code: ^{131}I -MIBG

Molecular/Structural formula:



Appearance: Clear, colorless liquid

Source: ^{131}I -MIBG is compounded by Nuclear Diagnostic Products, Rockaway, New Jersey upon prescription by physician at UCSF (University of California, San Francisco).

Each dose is prepared for administration for a particular patient as prescribed.

2. Name and Address of Compounding Pharmacy

Nuclear Diagnostic Products

101 Roundhill Drive

Rockaway, New Jersey 07866

Nuclear Diagnostic Products is a licensed nuclear pharmacy. It is licensed by the New Jersey State Board of Pharmacy and the NRC for compounding radioactive drugs.

3. Compounding and processing of ^{131}I -MIBG

3.1 Summary: Upon receiving a prescription for a particular patient by a physician at UCSF, ^{131}I -MIBG is compounded by iodination by heating at 155°C based on previously published methods^{1,2}. Ascorbic acid is added as a radioprotectant³. Free ^{131}I is removed by ion exchange if required. The product is sterilized by filtration. Quality control is ensured by Sep-Pak and ITLC and HPLC. The final product is shipped to UCSF. A further quality control test using Sep-Pak will be carried out at UCSF prior to administration. A percent tag of $\geq 93\%$ at UCSF will be ensured prior to administration. The product will be administered within three hours of performing the quality control (SepPak) at UCSF.

3.2 Materials and equipment used in the compounding process:

3.2.1 Materials used

- MIBG (Iodophenyl-methyl-guanidine hemisulfate) (ABX Advanced Biochemical Compounds, Radeburg, Germany)
- Cupric Sulfate Powder (Spectrum Chemicals, Gardena, CA), USP
- Ammonium Sulfate Powder (Spectrum Chemicals, Gardena, CA), FCC
- Ascorbic acid USP (Hospira, Inc, Rocky Mount, NC), USP

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- Sodium hydroxide (Spectrum Chemicals, Gardena, CA), NF
- Sterile Water for Injection (Hospira, Inc, Rocky Mount, NC), USP
- ^{131}I as sodium iodide solution (MDS Nordion, Ottawa, Canada)
- AG 1-X2 Resin (BioRad, Hercules, CA)

3.2.2 Equipment used

- Dose Calibrator – Capintec CRC15R
- Well counter – Ludlum 2200 Scaler with a Ludlum model 243 NaI detector
- Dionex Ultimate 3000 HPLC
- 0.22um filter –Millex SLGV033RS
- Sterile Vent Needle – BD Cat. # 305196
- Sterile Syringes 60ml – BD Cat# 309653
- Sterile Syringes 30 ml – BD Cat# 309650
- Sterile Syringes 20 ml – Bd Cat# 309661
- Sterile Blunt Needles – IMI Cat# 32-33
- Sterile Transfer Tubing – Wilburn Medical Cat# WUSA033
- Sterile Extension Set – Braun Cat# ET-30
- Three Way Valve – Braun Cat# D201 455991
- Fluid Transfer Sets – International Medical Industries, Inc. Cat. # (56-03)
- Reaction Vial-Hollister-Stier Cat # 7514ZA
- Heating Block –Labline, Model #2006
- Evacuated Vials – Hollister-Stier Cat. # 75142A
- Sterile 30ml glass vials – Hollister-Stier Cat. # 7520ZA
- Glass Beads- Kimble 13500-3
- Charcoal Trap Filtering System- is an in-house trap. The charcoal trap is an inhouse produced filter that is composed from standard ventilation products used to administer gases and aerosols in a hospital setting. A high performance bacterial/viral filter (Amici-Inc. 0822) is filled with charcoal and Dry-All (Amici-Inc 1012-1014). The filter is attached to a flexible ventilation hose (Amici-Inc) also filled with charcoal. Using a hose adaptor (Amici-Inc), this filter is attached to a second filter (Amici-Inc. 0822), with an injection stopper (Amici-Inc 184) on the opposite end.

3.3 Compounding Process

Iodination of MIBG is carried out as described below using an adaptation of the well-established ammonium sulfate enhanced exchange process¹.

3.3.1 Iodination

1. Activity of ^{131}I used is dependent on prescribed dose.
2. Amounts of MIBG, sodium iodide, copper sulfate (molar ratio of copper sulfate to ^{131}I is 1:4) and ammonium sulfate (500mg/ml) (volume ratio of ammonium sulfate to sodium iodide is 0.25:1) required are calculated based on activity required. 0.032 mg of MIBG per mCi ^{131}I is utilized. Amount of MIBG injected is well below the safe level referenced by USP DI for ^{131}I -MIBG used for imaging⁴.

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3. ^{131}I as sodium iodide is added along with copper sulfate, ammonium sulfate and MIBG to a sterile reaction vial to which sterilized glass beads are added (to increase surface for enhancement of MIBG drying).
4. An evacuated vial is connected to the charcoal trap filtering system. This serves as the overflow vial to capture vapor given off in the reaction.
5. The reaction vial is placed into the heating block with temperature set at 155°C
6. The vent tube (extension set) is immediately connected to the sterile overflow vial.
7. Mixture is heated for 120 minutes at 155°C .
8. At 10, 20 and 30-minute intervals 1 ml of air drawn from a clean air environment (laminar flow hood environment) is added to the reaction vial.
9. Reaction vial is removed from the heating block after 120 minutes and allowed to cool for 10 minutes.
10. Sterile Water for injection is added to the reaction vial and the contents are drawn into a Sterile syringe
11. The contents of the reaction vial are passed through the Ion Exchange column (see Section 3.3.2).
12. 0.4% sodium hydroxide is added in a volume equal to 2.5 times the volume of ammonium sulfate used.
13. 500mg ascorbic Acid is added to the solution.
14. The entire volume is withdrawn from the reaction vial into a syringe and filtered through a 0.22 μm filter for sterilization.
15. The product is transferred to a sterile 30-ml. glass vial.
16. Sterile water for injection is used to dilute the product and bring the final volume into a range of 32 to 34 ml. total volume.
17. Approximately 2 to 4mls are with drawn from the final product for quality control.
18. The product is assayed and the amount required to dose the patient is calculated.
19. Volume in the syringe is adjusted to obtain the desired amount of millicuries needed.
20. The volume lost in dosage adjustment is replaced with sterile water to make a final volume of 30ml.

3.3.2 Ion Exchange (if required)

Free ^{131}I is removed utilizing an ion exchange column.

3.3.2.1 Preparation of the Ion Exchange Column

1. A 30mL sterile glass vial is opened in a laminar flow hood with use of a crimper.
2. Approximately 0.250g AG 1-X2 Resin is placed in an open sterile vial and 5 to 10 ml. of sterile water for injection is added.
3. Resin is added to the ion exchange column and washed with sterile water for injection until 0.8 ml resin is retained in the column...
4. Column containing resin is autoclaved and placed in a laminar flow hood.
5. Column is washed with sterile water for injection.

3.3.2.2 Ion Exchange

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1. 10 to 20 ml of sterile water for injection is added to the reaction vial and the contents are drawn off into a syringe.
2. Labeled ^{131}I -MIBG is added to the top of the ion exchange column.
3. The labeled product is collected from the bottom of the column into a sterile syringe.

3.4 Sterilization of Product

Sterilization is performed by passing the contents of the reaction vial through a 0.22-micron sterilization filter and collection into a sterile syringe.

4. Finished Product Specifications and Test Methods at source prior to dispensation:

The finished product is ^{131}I -MIBG with 500mg ascorbic acid as a radioprotectant

- A. Appearance: Clear, colorless solution
- B. Volume: approximately 30 ml
- C. Amount of activity: as prescribed
- D. Labeling efficiency : >98% on ITLC and Sep-Pak and HPLC
- E. Sterile for bacteria.
- F. Non-pyrogenic: Endotoxin <1.25 EU/ml
- G. The finished product will be placed in a -70 freezer for one hour to achieve a frozen state for transportation.

4.1 Finished product packaging

The finished product will be dispensed in a 30ml sterile vial, Hollister-Steir Cat.# 7520ZA. The container will be labeled with the information described in Section 10 affixed to the container. The vial will be placed in a lead-lined container for transport to UCSF.

5. Transport to UCSF

^{131}I -MIBG is transported to UCSF in an insulated travel container containing Dry Ice.

6 . Pre-administration testing at UCSF

To ensure labeling efficiency at time of injection, Sep-Pak testing is carried out as described in 7.2.3.2 on approximately 0.005ml of sample (aspirated using sterile precautions). Prior to administration to the patient, Sep-Pak testing at UCSF will be carried out to insure that excessive radiolysis has not occurred. ^{131}I -MIBG will only be administered if the percent tag is $\geq 93\%$ at time of administration to the patient.

6.1 Product Specifications and Test Methods immediately prior to administration

- A. Appearance: Clear, colorless solution
- B. Volume: approximately 30 ml
- C. Activity: as prescribed
- D. Labeling efficiency: Percent tag $\geq 93\%$ on Sep-Pak testing

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- E. Expiration time: Product will expire 3 hours after completion of labeling efficiency testing at UCSF.

7. Excipient Specifications and Test Methods:

7.1 Excipients are purchased from reputable suppliers and conform to specifications of the applicable compendia, such as USP, NF, or FCC. A certificate of analysis from the vendor will be kept on file for each lot of excipient and for test methods. The following documentation will be maintained accompanying the preparation sheet for each compounding of ¹³¹I-MIBG.

Ingredients	Lot Number
Reaction Vial	
Sodium iodide (¹³¹ I)	
MIBG stock solution	
Cupric sulfate	
Ammonium sulfate	
Sterile water for injection	
AG 1-X2 resin	
Ascorbic acid	

Test Methods	Lot Number
Sterility testing using QT Micro System	
Pyrosate Assay for pyrogens	
Sep-Pak	
ITLC	

7.2 Acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance.

The following quality control tests are carried out on the finished product at the compounding pharmacy:

7.2.1 Sterility testing

Sterility test on the product is performed using QTMicro System (Catalog # TM6100). Based on instructions provided by the manufacturer (Q.I. Medical, Nevada City, CA). Soybean-Casein Digest Medium growth media formulated according to USP XXVII requirements is used as growth medium. Negative test is failure of growth of microorganisms on medium for 14 days. Results of sterility testing will be communicated to clinicians at UCSF after 14 day incubation period is completed.

7.2.2 Pyrogen testing

Limulus Amebocyte Lysate (LAL) for Gel-clot Method (Pyrosate Assay, Associates of Cape Cod Inc, Falmouth, MA) is used for pyrogen testing. This will be a pass/fail for pyrogens at 0.25 EU/0.2ml. (<1.25 EU/ml).

7.2.3 Labeling efficiency

This is tested using the following methods:

7.2.3.1 ITLC

1. Silica Gel quality control strip Watman Cat# 440-222 ¼” by 2” is prepared
2. Solvent 50:1 ethanol and ammonium hydroxide solution is prepared
3. One drop of product is placed at ¼ inch from the bottom of the strip (Rf=0)
4. Strip is placed in the solvent (solvent level must be below the spotting point of product being tested)
5. Solvent is allowed to rise to the top of the strip
6. The strip is pulled away from the solvent and cut at Rf =0.75 (The top of the strip is the spotting point is 0.0).
7. The bottom part of the strip is placed in test tube “A” (tagged MIBG)
8. The top of the strip is placed in test tube “B” (Free Iodide)
9. Percent tag = $A/(A+B)*100$
10. Product is dispensed only if the percent tag is 98% or greater

7.2.3.2 Sep-Pak Method. This is based on previously described methods for quality control of ¹³¹I-MIBG42.

1. Sep-Pak (Waters Sep-Pak cartridges, Milford, MA) is prepared by pushing 5ml. of 95% ethanol through the Sep-Pak
2. 5 to 10ml. of distilled or sterile water for injection is pushed through the Sep-Pak
3. Approximately 0.005ml of product is added to the top of the Sep-Pak
4. Sep-Pak column is flushed with 5ml. of distilled water (free Iodide will elute through)
5. Cartridge is placed in a test tube and counted in a well counter (A)
6. 5ml of distilled water from the flush is also counted in the well counter (B)
7. Percent tag = $A/(A+B)*100$
8. Product is dispensed only if the percent tag is 98% or greater.

7.2.3.3 HPLC

Mobile phase: – Prepare a filtered and degassed mixture of water and acetonitrile (900:100). Add 4.04 g of triethylamine per liter, and adjust with phosphoric acid to a pH of 4.0 ± 0.4 . Make adjustments if necessary.

Standard preparation: - Dissolve and accurately weighed quantity of iobenguane sulfate in water to obtain a solution having a known concentration of about 1mg per ml

Test Preparation – Use Iobenguane 1-¹³¹ Injection

Chromatographic system: - The liquid chromatograph is equipped with a 229 –nm detector, a collimated radiation detector.

Procedure: - Inject a volume (about 20uL) of injection, equivalent to between 1.6 and 2.7 MBq (or between 33 and 64 uCi) into the chromatograph, record the chromatograms, and

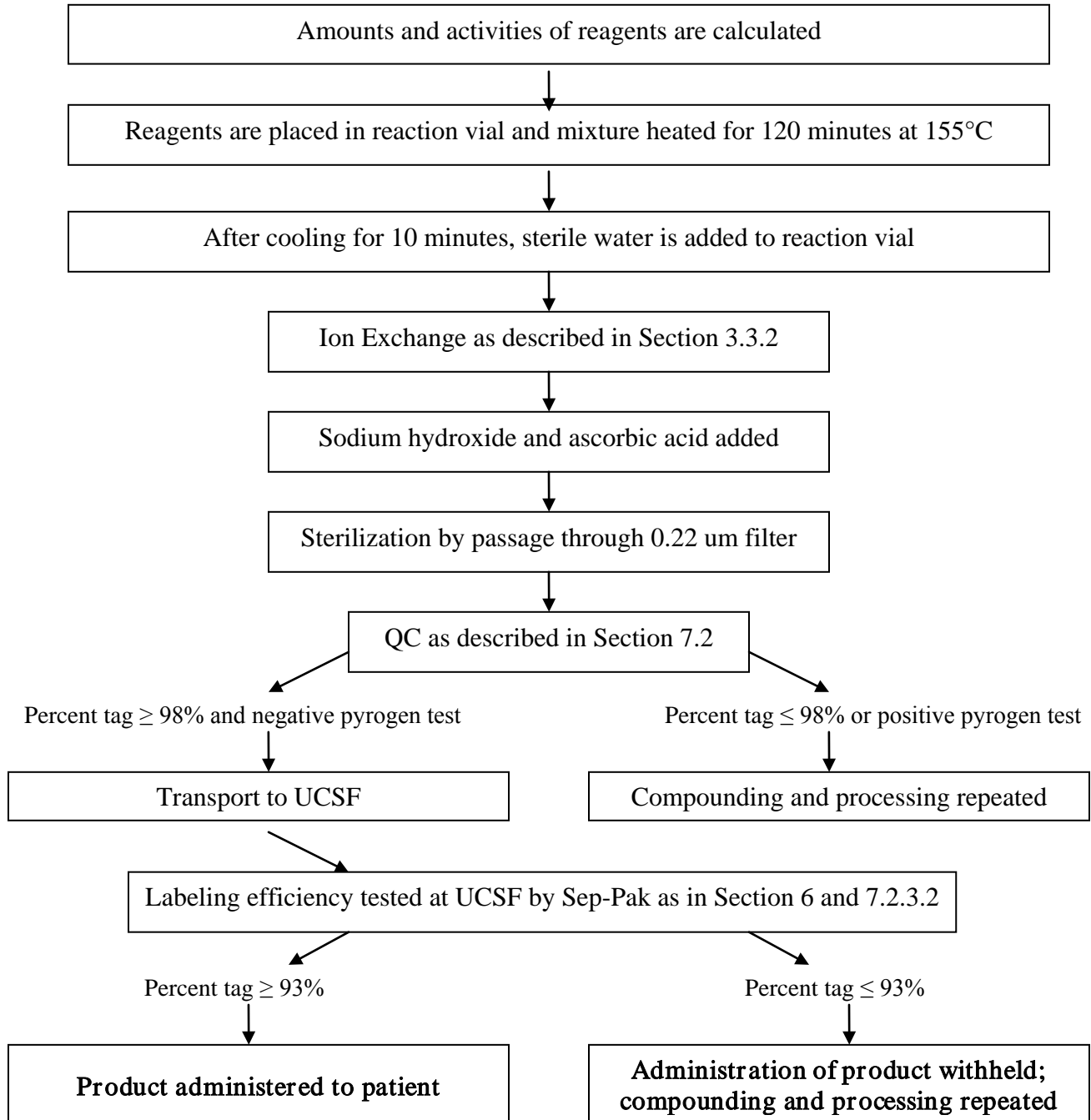
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measure the areas for the major peaks. The results of the chromatograph will meet or exceed the USP limit for this product. The Product will only be dispensed to UCSF if percent tag is determined to be $\geq 98\%$ on ITLC, Sep-Pak Methods and HPLC.

8. Flow Chart

The following flow chart summarizes the steps in the compounding and QC processes prior to administration of ¹³¹I-MIBG. Steps are detailed in Section 3.3.1



9. Stability Testing

¹³¹I-MIBG stability has been tested by assessing retained radioactivity at various time intervals after radioiodination. Sep-Pak test was performed on ¹³¹I-MIBG kept at room temperature at 2 to 48 hours after iodination. With the addition of 50 to 1000mg of ascorbic acid added to 30ml of ¹³¹I-MIBG, the percent tag was not significantly diminished at 48 hrs post-radioiodination.

Amount of ascorbic acid	Time after radioiodination	% tag
50mg	0 hours	99.2
250mg	0 hours	99.7
500mg	0 hours	99.5
1000mg	0 hours	99.8
50mg	5.5 hours	99.4
250mg	4 hours	99.7
500mg	5.5 hours	98.6
1000mg	5.5 hours	99.4
50mg	22 hours	80.3
250mg	22 hours	98.2
500mg	22 hours	98.7
1000mg	22 hours	99.1

Stability was also preformed on the frozen product. Sample one and three were frozen for 22 hours at -70c. and samples 2 and 4 were frozen for 45 hours at -70c. The product was thawed at room temperature for one hour and quality control was preformed at various intervals with the product stored at room temperature. The data supports that the ¹³¹I-MIBG is stable for 45 hours when frozen and maintains an acceptable level of binding for 4 hours after thawing.

Frozen Data

Sample 1 – 62mg	0 hours	99.7
Sample 1	23 hours (22 hours at -70c)	94.3
Sample 1	45 hours (22 hours room temp.)	72.4
Sample 1	48 hours (26 hours room temp.)	65.8
Sample 2 - 62 mg	0 hours	99.8
Sample 2	45 hours (44 hours at -70c)	94.6
Sample 2	48 hours (4 hours at room temp.)	94.5
Sample 3 – 500 mg	0 hours	99.6
Sample 3	23 hours (22 hours at -70)	97.3
Sample 3	45 hours (22 hours at room temp.)	87.0
Sample 3	48 hours (26 hours at room temp.)	84.5
Sample 4 – 500 mg	0 hours	99.6
Sample 4	45 hours (44 hours at -70c)	99.7
Sample 4	48 hours (4 hours room temp.)	98.6

10. Labeling

A copy of all labels and labeling to be provided to each investigator

Label for ¹³¹I-MIBG will contain the following information:

Sponsor's name: University of California, San Francisco

Product name: ¹³¹I-metaiodobenzylguanidine

Patient's name:

Rx Number

Dose:

Caution: New drug limited by Federal Law to investigational use.

11. Sample Certificate of Analysis

Sample Certificate of Analysis will contain the following information:

Name of patient

Prescribing physician

Date

Product name: ¹³¹I-metaiodobenzylguanidine

Product specifications:

Principal Investigator: Paul A. Fitzgerald, M.D.
Compassionate Use of ¹³¹I-MIBG for Patients with Malignant Pheochromocytoma

Rx number

Dose

Appearance: clear, colorless

Ascorbic acid 500 mg

Sterile water for injection USP

Volume: 30 ml

Labeling efficiency on ITLC:

Labeling efficiency on Sep-Pak

Results of Pyrosate Assay: pass

Results of sterility testing by QT Micro System assay: will be entered after 14 day incubation period is complete.

11.1 Other Documentation

Results of Sep-Pak testing carried out at UCSF will be documented. Records will be maintained at UCSF Radiopharmacy.

Results of sterility testing will be communicated to UCSF physicians and records maintained both at UCSF Radiopharmacy and at Nuclear Diagnostics Products.

1. Wafelman AR, Konings MC, Hoefnagel CA, Maes RA, Beijnen JH. Synthesis, radiolabelling and stability of radioiodinated m-iodobenzylguanidine, a review. *Appl Radiat Isot.* Oct 1994;45(10):997-107.
2. Mock BH, Weiner RE. Simplified solid-state labeling of 123m-iodobenzylguanidine. *Appl Radiat Isot.* 1988;2:92-942.
3. Chakrabarti MC, Le N, Paik CH, De Graff WG, Carrasquillo JA. Prevention of radiolysis of monoclonal antibody during labeling. *J Nucl Med.* Aug 1996;37(8):114-118.
4. USP DI for Iobenguane.