



DePaul Health Center

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12-11-07

Materials Licensing Section
U.S. Nuclear Regulatory Commission, Region (III)
2443 Warrenville Rd STE 210

Lisle, Ill 60532-4352

Re: License Amendment Application for License No. 24-02490-03

DePaul Health Center is requesting that your office amend its license, adding therapy with the GliSite catheters and Iotrex for brain tumor patients. Attached to this letter you will find documents specific to this request.

If you have any questions regarding this application, please contact me at (314) 344-6090. Thank you for your consideration.

A handwritten signature in black ink, appearing to read 'Thomas P. Bocchini'.

Thomas Philip Bocchini, M.D
Radiation Safety Officer

RECEIVED JAN 03 2008

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Request for Amendment of the DePaul Hospital

Radioactive Materials License

To Add the Cytac Surgical Products' Gliasite® Brachytherapy Systems

Specifically, this licensee wishes to add the following line item to our license:

Material in 10CFR35.1000

- **Radionuclide:** I-125
- **Physical Form:** an aqueous solution containing Na-3-[I-125] Iodo-4-hydroxybenzenesulfonate (Iotrex)
- **Inventory Limit:** as needed (or 8 Ci)
- **Purpose:** Brachytherapy with the Gliasite catheter

This line item amendment request follows the format and content of the NRC guidance published on the NRC web page (<http://www.nrc.gov/materials/miau/med-use-toolkit/liquid-brach.html>).

Liquid Brachytherapy Sources and Devices

Licensing Guidance – I-125 Iotrex™ Liquid Brachytherapy Source in Cytac Surgical Products' Gliasite® Radiation therapy System:

The licensee is requesting a line item amendment to use the Cytac Surgical Products' Gliasite Catheters and Iotrex. Iotrex is a liquid brachytherapy radioactive source and the Gliasite catheters are used to temporarily contain the Iotrex during brachytherapy. The Gliasite catheters are listed on the U.S. NRC Sealed Source and Device Registry (GA-1148-D-101-S).

1. Cytac Surgical Products will provide training for the authorized user(s) prior to the licensee performing the first brachytherapy procedure using the Gliasite in patients.
2. The licensee will have an authorized physician user with experience in radiopharmaceutical therapy procedures available "on call" to provide guidance and assistance in case of actual or suspected leakage of the implanted device.
3. Per our Written Directive for brachytherapy with the Gliasite, the "prescribed dose" is the prescribed radiation dose, in units of Gy delivered.



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4. Our Written Directive for brachytherapy with the GliaSite catheters includes the nuclide (I-125), the chemical/physical form (Iotrex), prescribed radiation dose (Gy), administered dosage of Iotrex (mCi) and dwell time (hours).
5. Prior to afterloading the Iotrex, the integrity of the GliaSite catheter will be determined using one of a variety of imaging modalities such as MRI, CT or radiographs. The images will be obtained with the GliaSite catheter inflated, demonstrating the continued capability of the catheter to maintain its inflated fluid volume. The images used in this assessment will be kept in the patient's medical records as required by state regulations.

For patients treated during brachytherapy on an outpatient basis, we will follow the model guidance provided in US NRC NUREG – 1556, vol. 9, Appendix U in releasing these patients for the duration of their brachytherapy treatment, making only the minor changes made necessary to satisfy 10 CFR 35.1000. Documentation demonstrating compliance with Section 35.75 requirements that the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 mSv is provided. Documentation includes forms describing the evaluation process for determining which patients are suitable for outpatient treatment, calculation for duration of outpatient release, patient release justification, and appropriate patient instructions (see attachments A-D).

6. The licensee will evaluate all events which occur involving the unexpected loss of retained radioactivity in the catheter and assess the dose to the critical organ (bladder wall, per Iotrex Package Insert). If the dose to the critical organ exceeds 50 rem, the event will be handled and reported as a misadministration.

Per the manufacturer's product information, a small quantity of radioactivity diffuses from the catheter during normal operation.

The licensee will evaluate each patient treatment to determine if the prescribed dose was successfully delivered to the treatment site. Specifically, a delivered radiation dose that differs by more than 20% from the prescribed radiation dose will be evaluated as a medical event.

7. Diagnostic quality images will be obtained with the GliaSite catheter inflated, demonstrating the continued capability of the catheter to maintain its inflated fluid volume. The images used in this assessment will be kept in the patient's medical records as required by state regulations. The leak tests typically required by brachytherapy sources (e.g., removable contamination) are not possible as the GliaSite catheter is completely subcutaneous while the radioactive material resides within it. Also, the SDDR document states leak tests are not applicable to the GliaSite system.
8. The GliaSite catheter is a single use device that will not be inflated with Iotrex if the integrity of the device is not demonstrated prior to afterloading Iotrex. If it is determined

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that the balloon catheter leaked during brachytherapy, then it will be reported to the NRC within 5 days.

9. We will follow our policies and procedures for safe use of radioactive materials and provide instructions to the appropriate staff as necessary.

Thyroid bioassays will not be performed. Data from other institutions using the GliaSite RTS system demonstrate that air concentrations of radioiodine are below minimum detectable levels. In addition, no radioiodine uptake has been observed on thyroid bioassay at these facilities or during the initial safety and performance clinical trial.

10. The licensee will label syringes, syringe shields, vials and vial shields with the form of the byproduct material (e.g., I-125 Iotrex). Syringes and syringe shields will also include the procedure (e.g., GliaSite or brain brachytherapy).
11. The licensee will follow Cytoc Surgical Products' instructions regarding limitations on x-ray contrast concentration (e.g., < 25% by volume). At the conclusion of brachytherapy, compliance with the Written Directive will be demonstrated by volumetric retrieval of the afterloaded Iotrex (and saline) volume to within 80% of the volume infused at the start of brachytherapy.

Cytoc Surgical Products has determined that when a radiopaque dye with 330 milligrams of iodine per millimole of solution is diluted to a 25% strength solution, the GliaSite Balloon can still be imaged and the diluted dye will absorb less than 20% of the I-125 dose from the Iotrex. Therefore, if the licensee follows Cytoc Surgical Products' Instruction Manual and dilutes the radiopaque dye prior to every time the GliaSite Balloon is imaged, the licensee will not have to measure the activity of the Iotrex upon its removal from the patient. In this case, the volumetric measurement of the removed Iotrex can be used to determine whether the administration was in accordance with the written directive.

12. The licensee will return the licensed material to authorized recipients. In accordance with 10 CFR 30.41(a)(5), we will confirm that persons are authorized to receive byproduct material prior to transfer and:
- Retain the records needed to demonstrate that the package qualifies as a DOT Specification 7A container
 - Assemble the package in accordance with the manufacturer's instructions
 - Perform the dose rate and removable contamination measurements;
 - Label the package and complete the shipping papers in accordance with the manufacturer's instructions
 - Retain records of receipts and transfers in accordance with 10 CFR 30.51.



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Patient Information and Release Determination
(In conformance with US NRC NUREG-1556, Vol.9)
GliSite Therapy® with Iotrex®

V. Release Record of Radiation Exposure Rate (will be maintained for 3 years per 10 CFR 35.2075(a)).

Exposure Rate Measurement Data: Instrument Serial # Calibration date

Exposure rate: X' = mR/hr @ 1 meter Performed by:

Signature

- This patient was not releasable and therefore hospitalized.
This patient has reviewed all requirements for release, was given these written instructions and released.

Signature: (authorized user completing this form) Date:



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Calculation for Duration of Outpatient Release Using U.S. NRC NUREG-1556, Vol. 9 Criteria

In NRC NUREG-1556, Vol. 9, a patient may be released if the radiation dose to the individual most likely to receive the highest dose is less than or equal to 5 mSv. For this patient, the duration of release will be determined by the exposure rate at 1 meter from the patient, using the acceptable assumptions from NUREG-1556, Vol. 9.

Assumptions:

- 1.0 R equals 10 mSv (or 1.0 mR equals 0.01 mSv)
- Occupancy Factor, OF = 0.25 (for nuclides with $T_p > 1$ day)

The total dose for the most exposed person would be:

$$D = X'(\text{mR/hr}) * 0.01 (\text{mSv/mR}) * T(\text{hr}) * \text{OF}$$

$$D = 0.0025 * X' (\text{mR/hr}) * T (\text{hr})$$

Where;

D = dose to most exposed person (mSv)

X' = measured exposure rate at 1 meter (mR/hr)

T = outpatient duration (hr)

To maintain compliance with NUREG 1556, Vol. 9, D must be less than 5 mSv. The duration of outpatient release that complies with this requirement is found by solving the equation above for "T";

$$T_{\max} = 5 (\text{mSv}) / [X' (\text{mR/hr}) * 0.0025 (\text{mSv/mR})]$$

$$T_{\max} = 2000 / X'$$

Patient Name: _____ X' = _____ mR/hr @ 1 meter Dwell time, T = _____ hr
 Date: _____

$$T_{\max} = 2000/(X') = 2000/(\text{_____ mR/hr})$$

This patient can be released for outpatient therapy for the following amount of time:

T_{max} = _____ hours Does T_{max} exceed the desired dwell time? _____ Y/N

$$D = 0.0025(X')(T) = .0025*(\text{_____ mR/hr})*(\text{_____ hr})$$

For the desired dwell time (_____ hours) of outpatient therapy, the dose to the most exposed person is estimated to be:

$$D = \text{_____ mSv}$$

Example:

The exposure rate at 1 meter from a patient was measured as 7 mR/h and the desired dwell time is 120 hours. What is the maximum amount of time this patient can be released from the hospital? What would the exposed person's dose be?

$$T_{\max} = 2000/(X') = 2000 / 7 (\text{mR/hr})$$

$$T_{\max} = 285 \text{ hours (more than the desired dwell time)}$$

$$D = 0.0025(X')(T) = .0025*(7)*(120)$$

$$D = 2.1 \text{ mSv (under the release limit of 5 mSv)}$$



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Patient Information and Release Determination (In conformance with US NRC NUREG-1556, Vol.9) GliaSite Therapy® with Iotrex®

I. Patient Information

1. Patient Name: _____ 2. Date: _____ 3. Net Afterloaded Activity: _____ mCi
4. Sex: Male Female 5. Iotrex Afterloading date and time: _____ AM/PM
(circle one) (Date)
6. Iotrex Dwell Time: _____ hr 7. Date and time for return to hospital: _____ AM/PM
(circle one) (Date)
8. Karnofsky Performance Status: _____ (NOTE: if KPS less than 70, patient should remain hospitalized)
9. KPS evaluated by: _____ MD

II. Household Information for Duration of Outpatient Therapy

1. Who will transport patient between hospital and residence? _____
2. Contact numbers: _____
3. Household Members: Age: a. _____ b. _____ c. _____ d. _____ e. _____
Sex: a. _____ b. _____ c. _____ d. _____ e. _____

III. Patient Release Determination

Interview the patient to determine if the patient will adhere to the following instruction during the entire outpatient release. If the patient resides in an "Assisted Living" or "Nursing Facility" they are **not** a candidate for outpatient treatment.

Action for Patient	YES	NO
1. Sleep alone and keep a minimum distance of 6 ft. from other people sleeping. If possible sleep in a room by yourself.		
2. Do not return to work or participate in volunteer activities away from home.		
3. Maintain a prudent distance from other people as much as possible (e.g. > 3 feet)		
4. Keep the toilet especially clean by flushing twice after use. Men should sit during urination. Wash hands thoroughly after using toilet.		
5. Refrain from traveling by airplane or other mass transportation.		
6. Refrain from traveling by automobile except for trips to and from doctor/hospital.		
7. Avoid contact with children (<18 yrs.) and pregnant women. Keep a minimum distance of 10 ft.		
8. Terminate breast feeding (if applicable)		

The patient is potentially releasable if their KPS score is at least 70 and they answer all questions with "YES". If any question is answered "NO" or the KPS is less than 70, the patient will be hospitalized (go to Section VI).

IV. Instructions

1. Ensure the patient receives, understands and is willing to follow instructions: _____ Completed
2. Discuss procedures in case of emergency medical care: _____ Completed

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Patient Instructions: Outpatient Therapy with the GliSite® RTS

In order to release a patient undergoing radiotherapy with the GliSite RTS, written and verbal instructions should be given to the patient and understood by the patient. These instructions are meant to provide guidance in the good practices of radiation safety and contamination prevention for these patients.

For the duration of the outpatient therapy:

1. Sleep alone and keep a minimum distance of 6 feet from other people sleeping. If possible sleep in a room by yourself.
2. Do not return to work or participate in any volunteer activities away from home.
3. Maintain a prudent distance from other people as much as possible (e.g. > 3 feet).
4. Keep the toilet especially clean by flushing twice after use. Men should sit during urination. **Wash hands** thoroughly after using toilet.
5. Refrain from traveling by airplane or other mass transportation.
6. Refrain from traveling by automobile except for trips to and from doctor/hospital.
7. Avoid contact with children (< 18 yrs. old) and pregnant women. Keep a minimum distance of 10 ft.
8. Terminate breast feeding (if applicable)
9. **Remember to return to hospital on scheduled Date and Time:** _____ **AM/PM** _____
(circle one) (Date)
10. In case of emergency or if you have any questions, call _____
at _____

It is important to remember that these instructions are intended to keep yourself and others around you safe while you are at home during this radiation therapy treatment. Do not deviate from any of the above instructions.

I have received these instructions and fully understand them:

Patient signature	Date	Signature of responsible family member or guardian	Date
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These instructions were given by:

Signature (Authorized User or their Representative)	Date
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GliaSite Outpatient Therapy – Patient Release Justification

1. Radiation Exposures to Family Members and Caregivers

According to the NRC regulations (10CFR35.75) for releasing patients that were administered radioactive material, the criteria for releasing the patient is “the effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 millisieverts (0.5 rem).” Specific guidance in evaluating patients for release is given in NUREG 1556 Volume 9, Appendix U (hereafter referred to as “Appendix U”). Thus, procedures will be implemented that achieve this requirement. There are two situations that may result in exposure of others to the radiation from the patient. First, exposures will result from the low energy photons emitted by the I-125 contained in the patient’s body. Second, some level of exposure may occur from radioactivity excreted from the patient (urine is the only source of radioactivity excretion with the GliaSite and Iotrex).

The primary mode of radiation exposure will be from the low energy photons (photon energy <36 keV). Equation U.1 of Appendix U provides the basis for calculating the exposure of another person to radiation contained in the patient. However, instead of using an equation that has already been integrated over infinite time, and based upon the initially administered activity, in this case, one must integrate the exposure rate over the Iotrex dwell time (or duration of outpatient discharge, whichever is smaller). This total dose to an individual, based upon the measured initial exposure rate, is shown below:

The total dose for the most exposed person would be:

$$D = X' \text{ (mR/hr)} * 0.01 \text{ (mSv/mR)} * T \text{ (hr)} * OF$$

$$D = 0.0025 * X' \text{ (mR/hr)} * T \text{ (hr)}$$

Where;

D = dose to most exposed person (mSv)

X' = measured exposure rate at 1 meter (mR/hr)

T = outpatient duration (hr)

And we assume the following, per Appendix U:

- 1.0 R equals 10 mSv (or 1.0 mR equals 0.01 mSv)
- Occupancy Factor, OF = 0.25 (for nuclides with $T_p > 1$ day)

The maximum duration of outpatient release, T_{max} , that complies with this requirement is found by solving the equation above for T (hr);

$$T_{max} = 5 \text{ (mSv)} / [X' \text{ (mR/hr)} * 0.0025 \text{ (mSv/mR)}]$$
$$T_{max} = 2000 / X'$$

From this, it can be seen that the maximum outpatient release time interval (or the desired Iotrex dwell time) must be less than 2000 divided by the 1-meter exposure rate obtained following completion of the Iotrex afterloading procedure. Most Iotrex dwell times are 3-5 days (72-120 hours). Thus, based on the preceding dwell time range, patients can be released for this range of time provided the exposure rates are less than 27.8 mR/hr and 16.7 mR/hr at one meter, respectively. While these exposure rates are larger than those for permanent implants, recall that this is a short duration implant and higher exposure rates do not result in exposures above the regulatory limits. According to Proxima Therapeutics, typical exposure rates at 1 meter from the head are 2-3 mR/hr with the largest reported value less than 10 mR/hr. Thus, it is highly unlikely that exposures from GliaSite patients will exceed the regulatory limit. As an example, take a patient with a relatively long dwell time (144 hr) and high exposure rate (10 mR/hr). With the 0.25 occupancy factor, the exposure would be 3.6 mSv, a value below the regulatory limit.

The exposure one might receive from the slight amount of radioactivity excreted in the urine during normal operation of the device (<1% of the afterloaded activity) is negligible. Patients will be given explicit instructions on how to minimize potential for contamination. It is noted that the regulatory guidance in Appendix U explicitly disregards the potential radiation doses that might result from exposure or intakes of contamination activity, even for procedures that result in very large quantities of excreted activity (e.g., I-131 thyroid ablations with up to 200 mCi of I-131).

Therefore, we conclude that under normal operation of the device, radiation exposures to persons other than the family are unlikely to be above the regulatory limit. All patients who are to be released will undergo radiation exposure rate surveys and evaluation as to appropriateness for release (e.g., willingness to follow written and oral instructions) prior to release.

The other scenario to be evaluated is whether persons other than the patient might receive radiation exposures greater than 5 mSv in the event of a device failure during the outpatient time period. In this case, the majority of the radioactive material would be released from the GliaSite into the patient's body within a few hours of the failure. The chemical form of the I-125 in Iotrex is largely organically bound (>80%) or in the iodide form. It has been demonstrated that the organic form of the iodide is very rapidly and completely cleared from the body via the renal pathway¹. In humans it is anticipated that clearance would be essentially complete in 24-48 hours. As to the small portion of I-125 in the iodide form, the patient's thyroid is blocked prior to therapy. Therefore, the iodide is not accumulated in the body and is excreted in the urine with a rapid biological removal half-time (~8 hr). Thus, essentially all iodide-form I-125 would also be excreted in 24-48 hours. The patient's written and verbal instructions include double flushing of toilets (and the patient should have sole use of that toilet) and that men should sit to urinate. These guidelines were employed by the I-131 Bexxar® radioimmunotherapy agent and should practically eliminate the radiation exposure from contamination due to I-125 in the patient's urine. It should be noted that the patient release evaluation criteria stipulates that to be releasable, a patient must have a Karnofsky Performance Status (KPS) of 60 or greater. This level of performance means that the patient is largely autonomous and needs little or no assistance in caring for themselves. This also means that the patient is competent to handle excretory functions autonomously. Therefore, the opportunity for family members or caregivers to come into contact with highly radioactive urine is minimal.

Therefore, under both normal operation and complete failure scenarios, radiation exposures to family members or caregivers, from radiation/radioactivity of a GliaSite patient (temporary outpatient release) are unlikely to exceed the regulatory limit of 5 mSv. In all cases, patients released, as well as their caregivers, will be evaluated for appropriateness for release (performance status, willingness to follow instructions) and given the proper instructions to maintain radiation exposures to within regulatory limits.

2. Assessing Device Integrity Following Afterloading

It was noted that the NRC requests a methodology for assessing the GliaSite's integrity for holding Iotrex during brachytherapy. In response, we note and propose the following. First, as shown above, regardless of whether the GliaSite functions properly during brachytherapy, or undergoes a complete loss of radioactivity, the radiation exposures to the person most likely to receive the highest radiation exposure will be less than the regulatory limit of 5 mSv. Upon completing the Iotrex afterloading and during brachytherapy, radiation exposure rate measurements will be used to monitor for unexpected leakage of radioactive material from the GliaSite catheter. Radiation measurements will be performed over the injection site surface (at 20 to 30 centimeters from the injection site), at 1 meter from the injection site, and over the patient's bladder. These measurements establish baseline, normal operational parameters for exposure rates.

The design validation studies required for FDA clearance and sealed source device registration showed that the balloon can withstand more volume cycling (inflation/deflation) than is seen clinically without adverse effects on the functionality of the catheter (personal communication – James B. Stubbs, Ph.D, Chief Technology Officer for Proxima Therapeutics). As per the device's instruction manual, several quality assurance steps are performed on the device's fluid integrity prior to brachytherapy to insure the GliaSite has not developed nor will develop a fluid

¹ Stubbs JB, Strickland AD, Frank RK, Simón J, McMillan K and Williams JA: Biodistribution and Dosimetry of an Aqueous Solution Containing Sodium 3-(¹²⁵I)iodo-4-hydroxybenzenesulfonate (Iotrex™) for Brachytherapy of Resected Malignant Brain Tumors. *Cancer Biotherapy and Radiopharmaceuticals* 15:645-656, 2000.

integrity failure mode. Specifically, these QA steps are; fluid inflation prior to implant in the operating room, fluid inflation under visual inspection in the surgical cavity at time of implant, MRI (or other imaging modality) of the inflated catheter several days after surgery (prior to brachytherapy), and fluid retrieval and saline-rinsing of the balloon immediately prior to afterloading Iotrex.

Thus, having successfully passed all pre-therapy QA tests, the patient proceeds to brachytherapy (obviously, if any QA step is failed, the device is not loaded with Iotrex). We will afterload the Iotrex in the patient while the patient is in the hospital. We propose, as an additional QA step, to keep the patient in the hospital for an appropriate amount of time (approximately 1- 2 hours) following the afterloading and repeat the radiation surveys. Any significant changes from the initial readings (e.g., large decrease in cranial exposure rates [e.g., >35% drop] concomitant with large increases in bladder exposure rates [e.g., >30-fold increase]) will be documented and evaluated for further action as appropriate (e.g., patient not released from the hospital). Exposure rate surveys will be performed using survey meters appropriate for measuring exposure rates from low energy photon sources such as I-125. If the exposure rate surveys are consistent between baseline and the delayed set, the patient will be released upon meeting the evaluation and agreeing to the instructions.

DePaul Health Center
12303 DePaul Dr
Bridgeton, MO 63044
Radiation Oncology

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US Nuclear Regulatory Commission
Region III
2443 Warrenville Rd STE 210
Lisle, IL
60532-4352

