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May 17, 2007

United States
Nuclear Regulatory Commission
Medical Licensing Branch
475 Allendale Road
King of Prussia, PA 19406

Re: Line Item Amendment for Outpatient Therapy with the GliaSite® RTS & Iotrex®

To Whom It May Concern:

03002502

Saint Peter's University Hospital is seeking a line item amendment to its U.S. NRC radioactive material license, 29-07566-01, adding outpatient therapy with the GliaSite catheters and Iotrex for selected and appropriate brain tumor patients. We will adhere to the guidance of the US NRC NUREG-1556, Vol.9 along with the following statements and attachments in releasing these patients for the duration of their brachytherapy. The "GliaSite Outpatient Therapy – Patient Release Justification" was developed by Proxima Therapeutics, in compliance with NUREG-1556, Vol 9 requirements that the most likely exposed person will not receive a radiation dose in excess of the regulatory requirement (5 mSv).

1. The patients will be instructed to proceed directly home and to remain within their house and yard for the duration of brachytherapy. It is part of the written instructions for the patient to not return to work and to avoid prolonged contact with other people. A total of 8 instructions are given in writing to insure that exposures to members of the public are kept to within the NRC requirements. See the attachment "Patient Instructions".
2. When the patient is in the hospital for brachytherapy, we will restrict the patient to their room to minimize radiation exposures to other people in the hospital. On an outpatient basis, we will instruct the patient to stay within the confines of their home/yard and stress the proper actions to limit exposures to members of the general public. See the attachment "Patient Instructions".
3. We commit to releasing patients only after they are evaluated for release and found willing to abide by the instructions given prior to release, which includes acknowledgement by the patient of the date and time of return. The patient evaluation form clearly indicates the time and date of patient return. In addition, the written instructions given to the patient to take with them at release clearly provide the time and date of return, in larger font and bold typeface. Hence, we will have confidence that the patient will return and is competent to understand the importance of returning, or the patient will not be released. See the attachments "Patient Information and Release Determination" and "Patient Instructions".
4. We concur with the patient release rationale and justification, as provided by Proxima Therapeutics (authored by Dr. James Stubbs). See the attachments "Calculation for Duration of Outpatient Release" and "Patient Release Justification".

140559

NMSS/RGN1 MATERIALS-002



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If you have any questions, please call Robert J. Tokarz, RSO at 732-424-0909.

Sincerely,

A handwritten signature in black ink, appearing to read "Anthony Costabile".

Anthony Costabile,
Vice President Professional Services

- Enclosure: **Patient Information and Release Determination Form**
- Patient Instructions for Outpatient Therapy**
- Calculation for Duration of Outpatient Release**
- GliaSite Outpatient Therapy – Patient Release Justification**

MKT 0084 Rev A

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

Saint Peters University Hospital

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 10 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

V. Release Record of Radiation Exposure Rate (should be maintained for 3 years per 64E-5)

Exposure Rate Measurement Data: _____
Instrument Serial # Calibration date

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

VI. 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: _____ Date: _____
(authorized user completing this form)

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 10 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

These instructions were given by:

Signature (Authorized User or their Representative)

Date

Calculation of 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";

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

$$T_{\text{max}} = 2000 / X_-$$

Patient Name: _____ $X_- =$ _____ mR/hr @ 1 meter Dwell time, T = _____ hr
Date: _____

$$T_{\text{max}} = 2000/(X_-) = 2000/(\text{_____ mR/hr})$$

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

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

$$D = 0.0025(X_-)(T) = .0025*(\text{_____ mR/hr})*(\text{_____ hr})$$

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?

$$T_{\text{max}} = 2000/(X_-) = 2000 / 7 (\text{mR/hr})$$

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

$$D = 0.0025(X_-)(T) = .0025*(7)*(120)$$

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

GliaSite Outpatient Therapy – Patient Release Justification

1. Radiation Exposures to Family Members and Caregivers

According to the NRC regulations (10CFR35.75) for releasing patients 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:

$$D = X_{-} (\text{mR/hr}) * 0.01 (\text{mSv/mR}) * T(\text{hr}) * \text{OF}$$

$$D = 0.0025 * X_{-} (\text{mR/hr}) * T (\text{hr})$$

Where;

D = dose to most exposed person (mSv)

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

T = outpatient duration (hr)

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);

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

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 GliSite 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 GliSite 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 GliSite's integrity for holding Iotrex during brachytherapy. In response, we note and propose the following. First, as shown above, regardless of whether the GliSite 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 GliSite 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 cyclings (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 GliSite 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 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.

This is to acknowledge the receipt of your letter/application dated

5/17/2007, and to inform you that the initial processing which includes an administrative review has been performed.

Answer, 29-07566-01
There were no administrative omissions. Your application was assigned to a technical reviewer. Please note that the technical review may identify additional omissions or require additional information.

Please provide to this office within 30 days of your receipt of this card

A copy of your action has been forwarded to our License Fee & Accounts Receivable Branch, who will contact you separately if there is a fee issue involved.

Your action has been assigned **Mail Control Number** 140554.
When calling to inquire about this action, please refer to this control number.
You may call us on (610) 337-5398, or 337-5260.