FACSIMILE TRANSMITTAL SHEET

To:	From:
Shirley Xu	Jean Gresick-Schugsta, M.S., D.A.B.R.
FAX NUMBER:	**Date:**
(610) 337-5269	June 2, 2006
COMPANY:	**TOTAL NO. OF PAGES INCLUDING COVER:**
US NRC Region 1	4
PHONE NUMBER:	**SENDER'S REFERENCE NUMBER:**
	Inspection for License No 37-07161-01
Re:	**YOUR REFERENCE NUMBER:**
Request for additional information	

☐ URGENT X FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Attached are copies of the derivation of the original calibration numbers for Sm-153 and Y-90, in accordance with the instructions included on each page.

The third page is a copy of the Zevalin instructions for the therapeutic dose using the Y-90 labeled material.

If you need additional information, please contact me.

Thank you.

Jean A. Gresick-Schugsta, RSO

YORK HOSPITAL - WELLSPAN HEALTH • 1001 SOUTH GEORGE STREET • YORK PA 17405
PHONE: 717-851-5166 • FAX: 717-851-4381

Pt. KATHRYN REED
Administer Intravenously

In-111 Activity: _____ mCi Volume: _____ ml

P.O. #: 28845

Once your department establishes a Y-90 syringe calibration factor, it should be used for all subsequent patient doses of Y-90 Zevalin of this volume.

If you have any questions, please call your local Syncor Pharmacy

DISPENSING PHARMACIST 6-25-02 DATE

Syncor
The word for trust. Worldwide.

NOTE: Your Radioactive Materials License may require that additional or other procedures be followed.

CRCISR = 1183 X 100

PROCEED

149,000 cells/mm³

M ALLOWABLE
90 ZEVALIN IS
(1184 MBq)

ravenously at an initial rate of 50 mg/hr.
on-related events do not occur,
400 mg/hr. If hypersensitivity or an
ed (see WARNINGS). The infusion

5.0 mCi (1.6 mg total antibody dose)
micrometer low-protein-binding filter
ZEVALIN. After injection, the line

ep 1 administrations.

an initial rate of 100 mg/hr (50 mg/hr if
d increased by 100 mg/hr increments

f 0.4 mCi/kg (14.8 MBc/kg) actual body
y/kg) actual body weight for patients
a period of 10 minutes. A 0.22
sion port prior to injection of Y-90
no. Precautions should be taken to
IN injection. Close monitoring for
is or symptoms of extravasation have
. **The prescribed, measured, and**
vable dose of 32.0 mCi (1184 MBq),
th a platelet count <100,000/mm³

lfolabeling procedure. Important,
ne Y-90 ZEVALIN dose.

am immediately prior to
anufacturer's specifications and

employed. Waterproof gloves should
I-111 ZEVALIN. Appropriate shielding
ng administration to the patient. The

Mallinckrodt, Inc.

TION, Zevalin Therapeutic Regimen

11 ZEVALIN. The use of high purity
ired.

temperature. Note: The ZEVALIN
ese particulates will be removed by

vial with a suitable alcohol swab and

) room temperature). To avoid the
withdraw 10 mL of air from the

7. Transfer 5.8 mCi of In-111 chloride to the Reaction Vial with a sterile 1 mL syringe. Mix the two solutions and coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

8. With a sterile 3 mL syringe, transfer 1.0 mL of ZEVALIN (ibritumomab tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by gentle inversion or rolling. **Do not shake or agitate the vial contents, since this will cause foaming and denaturation of the protein.**

9. Allow the labeling reaction to proceed at room temperature for 90 minutes. Allowing the labeling reaction to proceed for a longer or shorter time may result in inadequate labeling.

10. **Immediately** after the 30-minute incubation period, using a sterile 10 mL syringe with a large bore needle (18 G - 20 G), transfer the calculated volume of Formulation Buffer from step 5.c. to the Reaction Vial. Gently add the Formulation Buffer down the side of the Reaction Vial. If necessary, to normalize air pressure, withdraw an equal volume of air. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not shake or agitate the vial contents. Avoid foaming.

11. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume, and the date and time of expiration, and affix these labels to the reaction vial and shielded reaction vial container.

12. Calculate the volume required for an In-111 ZEVALIN dose of 5 mCi. Withdraw the required volume from the Reaction Vial contents into a sterile 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The syringe should contain the dose of In-111 ZEVALIN to be administered to the patient. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume added, and the date and time of expiration, and affix these labels to the syringe and shielded unit dose container.

13. Determine Radiochemical purity. See Section C: Procedure for Determining Radiochemical Purity Section that follows DIRECTIONS FOR PREPARATION OF THE Y-90 ZEVALIN DOSE.

14. Store Indium-111 ZEVALIN at 2-8°C (36-46°F) until use and administer within 12 hours of radiolabeling.

15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen Administration: Step 1

16. Discard vials, needles and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

B. PREPARATION OF THE Y-90 ZEVALIN DOSE

GENERAL:
Read all directions thoroughly and assemble all materials before starting the radiolabeling procedure. Important, significant differences exist in the preparation of the In-111 ZEVALIN dose and the Y-90 ZEVALIN dose.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of Y-90.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized in the preparation and during the determination of radiochemical purity of Y-90 ZEVALIN. Appropriate shielding should be used during radiolabeling, and use of a syringe shield is recommended during administration to the patient. The radiolabeling of ZEVALIN shall be done according to the following directions.

Required materials not supplied in the kit:

A. Yttrium-90 Chloride Sterile Solution from MDS Nordion (shipped directly from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit)
B. Three sterile 1 mL plastic syringes
C. One sterile 3 mL plastic syringe
D. Two sterile 10 mL plastic syringes with 18-20 G needles
E. Instant thin-layer chromatographic silica gel strips (ITLC-SG)
F. 0.9% sodium chloride aqueous solution for the chromatography solvent
G. Suitable radioactivity counting apparatus
H. Developing chamber for chromatography
I. Filter, 0.22 micrometer, low-protein-binding (see DOSAGE AND ADMINISTRATION, ZEVALIN Therapeutic Regimen Administration)
J. Vial and syringe shield

Method:

1. Sterile, pyrogen-free Y-90 chloride must be used for the preparation of Y-90 ZEVALIN. The use of high purity Y-90 chloride manufactured by MDS Nordion is required.

2. Before radiolabeling, allow the contents of the refrigerated carton to reach room temperature. Note: The ZEVALIN vial contains a protein solution that may develop tragelucent particulates. These particulates will be removed by filtration prior to administration.

3. Clean the rubber stoppers of all of the vials in the kit and the Y-90 chloride vial with a suitable alcohol swab and allow to air dry.

4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to room temperature). To avoid the buildup of excessive pressure during the procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.

5. Prior to initiating the radiolabeling reaction, determine the amount of each component needed according to the directions below:

   a. Calculate the volume of Y-90 chloride that is equivalent to 40 mCi based on the activity concentration of the Y-90 chloride stock.

   b. The volume of 50 mM sodium acetate solution needed is 1.2 times the volume of Y-90 chloride solution determined in step 5.a., above. (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction.)

   c. Calculate the volume of Formulation Buffer needed to bring the Reaction Vial contents to a final volume of 10 mL. This is the volume of Formulation Buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example if the volumes were 0.5 mL of Y-90 chloride, 0.6 mL of sodium acetate and 1.3 mL of ZEVALIN, then the amount of formulation buffer would be 10 - (0.5 + 0.6 + 1.3) = 7.6 mL.

6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM sodium acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

12. Calculate the volume required patients with normal plate count of 100,000 - 149,000 must not exceed the absol body weight. Withdraw the large bore needle (18 G - 20 operated in accordance with The syringe should contain 10% of the actual prescribed ± 10% of the prescribed dose preparation, the total activity syringe and shielded unit dos

13. Determine Radiochemical Pu follows these DIRECTIONS F

14. Store Yttrium-90 ZEVALIN at

15. See DOSAGE AND ADMINIS

16. Discard vials, needles and sy and biohazardous waste.

Yttrium-90 ZEVALIN is suitable for admin preparation and injection, no special shie

C. PROCEDURE FOR DETERMINING
The following procedure should be

A. At room temperature, place a strip.

B. Place the ITLC-SG strip into a top. Allow the solvent (0.9% N the chamber and cut the strip counting apparatus.

C. Calculate the percent RCP

$$\% \text{ RCP} = \frac{\text{CPM bo}}{\text{CPM bottom hal}}$$

D. If the radiochemical purity is radiochemical purity is <95%

IMAGE ACQUISITION AND INTERPRE
The biodistribution of In-111 ZEVALIN sh posterior gamma images. A set of imag images at other timepoints may be nece equipped with a medium energy collimat field-of-view gamma camera and mediu energy photopeaks set at 172 and 247 k 7-10 cm/min for subsequent scans.

EXPECTED BIODISTRIBUTION
Visual inspection of the required gamma

- Activity in the blood pool areas
- Moderately high to high uptake
- Moderately low or very low upt
- Non-fixed areas within the bowe be necessary to confirm gastroi
- Focal fixed areas of uptake in t

Tumor uptake may be visualized in soft ti may be seen as areas of increased or dec Y-90 Zevalin therapy.

ALTERED BIODISTRIBUTION
The criteria for altered biodistribution are n images:

- Intense localization of radiotrace uptake.
- Increased uptake in normal org
  - Diffuse uptake in normal liv
  - Kidneys have greater inten
  - Fixed areas (unchanged wi
  - In less than 0.5% of patient characterized by clear visu

If a visual inspection of the gamma image ZEVALIN dose. The safety and efficacy o not known. Possible causes of prominent marrow activity due to recent hematopoiet with HAMA and HACA, should be consid be performed. Y-90 ZEVALIN should not repeat biodistribution scans.

During ZEVALIN clinical development, indi been reported. Although solid organ toxic consideration should be applied before pr organs or structures.

Unit Dose Calibration Factor Form

Zevalin™
In111 and Y90
Ibirtumomab Tiuxetan

Geometry Consideration
for Dose Calibrators

Syncor Pharmaceutical Services

IMPORTANT NOTE: Because Yttrium 90 (Y-90) is a pure beta emitter, care must be exercised when making dose activity measurements in a dose calibrator. The accurate measurement of Y-90 is <u>geometry</u> and <u>container</u> dependent.

Syncor's dose calibrators have been tested and adjusted to measure Y-90 accurately through the use of a National Institute of Standards and Technology (NIST) source of Y-90. All patient doses are dispensed in a 10 ml plastic syringe to maintain dose activity measurement accuracy.

You must establish a Y-90 syringe calibration factor for your dose calibrator. To do so, place this syringe in your dose calibrator. Manually select a calibration factor using the button or knob until the activity displayed matches that on the prescription at the stated calibration time.

Syncor Int'l Corporation
Pharmacy Service Center • 8191 Presidents Drive
Hummelstown PA 17036

[redacted] Rt 02 Run
25 MONUMENT RD
YORK , PA 17403-5048

Doctor CYNTHIA SHI # [redacted]

R [redacted]

Procedure	Date
NH-Lymphoma Therapy	25 JUN 02
Lot No.	**Expires**
Y90010-17601	06/25/02 18:??
Qty. Ordered [redacted]	
Assay 3.750 mCi/ml	**As Of** [redacted]
Volume [redacted]	**Dispensed By** [redacted] **Checked** [redacted]
Qty. Dispensed [redacted]	

Caution: To be used under the direct supervision of a physician.

Pt. KATHRYN REED

Administer intravenously

P.O. #: 293689

Syncor determined that this syringe had the following assay at the time of calibration using the listed syringe calibration factor.

Syncor Dose Calibrator:

Make: CAPINTEC

Model: 5-R

Serial Number: 51357

Y-90 Activity: 30 mCi Volume: 8 ml

Calibration Factor 56 x 10 *multiply displayed activity by 10

In-111 Activity: ______ mCi Volume: _____ ml

Once your department establishes a Y-90 syringe calibration factor, it should be used for all subsequent patient doses of Y-90 Zevalin of this volume.

If you have any questions, please call your local Syncor Pharmacy

[signature] 6-25-02
DISPENSING PHARMACIST DATE

NOTE: Your Radioactive Materials License may require that additional or other procedures be followed.

Syncor
The word for trust. Worldwide.

CRC15R = 1183 X100

Syncor
The Service Difference

Syncor Pharmacy Services

Quadramet®
Samarium Sm 153 Lexidronam Injection

GEOMETRY CONSIDERATIONS FOR DOSE CALIBRATORS

IMPORTANT NOTE: There will be differences in dose calibrator activity measurements from geometry variances between plastic syringes and glass vials containing Quadramet®.

You must establish a Sm-153 syringe calibration factor for your dose calibrator. To do so, place this syringe in your dose calibrator. Manually select a calibration factor using the button or knob until the activity displayed matches that on the prescription at the stated calibration-time.

Syncor determined that when this syringe was assayed using the syringe calibration factor of 269, it assayed 75.6 mCi at the time of calibration.

Once your department establishes a Sm-153 syringe calibration factor, it should be used for all subsequent unit doses of Quadramet®.

If you have any questions, please call your local Syncor Pharmacy.

Syncor Int'l Corporation
Pharmacy Service Center - 8181 Presidents Drive
Hummelstown PA 17036 717/566-2

[redacted] Rt 02 Run 1
25 MONUMENT RD
YORK , PA 17403-5048

Doctor SHEARER	# [redacted]
R [redacted] Rx	
Procedure Osseous Pain Therap	Date 06 OCT 00
Lot No. SM1531-27901	Expires 10/06/00 12:00
Qty. Ordered 75.00 mCi [redacted]	
Assay 24.500 mCi/ml	As Of [redacted]
Volume [redacted]	Dispensed By [redacted] Checked
Qty. Dispensed [redacted]	

Caution: To be used under the direct supervision of a physician.

Pt RUHLMAN

Administer Intravenously
For I.V. Administration Only

P.O. #: 216179

DISPENSING PHARMACIST

10-6-00
DATE

262009

mod 74.0 on orb "269" @ 11a