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Verluma™

Kit for the preparation of Technetium Tc 99m Nofetumomab Merpentan

For Intravenous Use Only

DESCRIPTION

Verluma™ is a kit for the preparation of Technetium Tc 99m Nofetumomab Merpentan, a diagnostic imaging agent for use by intravenous injection. Each kit contains one each of the non-radioactive components listed below, necessary to prepare one patient dose.

Container	Contents*
1	Isopropyl Alcohol, 99%, 1.5mL
2	Phenthioate Ligand (2,3,5,6-tetrafluorophenyl-4,5-bis-S-(1-ethoxyethyl)-thioacetoamidopentanoate), 0.28mg (dried)
3	Glacial Acetic Acid: 0.2 N Hydrochloric Acid 1:7 (v/v), contains 0.16mL
4	Stannous Gluconate Complex containing Sodium Gluconate, 45mg, and Stannous Chloride, Dihydrate, 0.79mg (lyophilized)
5	Reaction Vial - Empty, 10mL
6	1 M Sodium Bicarbonate Buffer, pH 10, 1mL
7	Nofetumomab (Fab fragment of murine monoclonal antibody NR-LU-10) in Phosphate Buffered Saline, 10mg in 1mL
8	Anion Exchange Column, 5mL with 0.2 µm Sterile Filter
9	Elution Vial - Empty, 10mL

* All components are sterile, pyrogen-free and do not contain preservative.

The active ingredient, Nofetumomab (Container 7), is the Fab fragment of an IgG2b murine monoclonal antibody NR-LU-10. The NR-LU-10 antibody is directed against an approximately 40kD glycoprotein antigen, that is expressed in a variety of cancers and some normal tissues. The NR-LU-10 antibody is produced by the serum-free, in-vitro fermentation of mammalian cells. Nofetumomab is derived from the enzymatic digestion of purified NR-LU-10 antibody with papain and is purified by chromatographic separation including viral inactivation and removal procedures.

The imaging agent is formed by combining the kit components with sodium pertechnetate Tc 99m (Technetium Tc 99m; see Dosage and Administration). Sterile and non-pyrogenic sodium pertechnetate Tc 99m from any generator source in 0.9% sodium chloride can be used.

As indicated in the directions provided, the isopropyl alcohol (Container 1) is used to dissolve the freeze-dried phenthioate ligand (Container 2). The phenthioate ligand (2,3,5,6-tetra-fluorophenyl-4,5-bis-S-(1-ethoxyethyl)-thioacetoamido-pentanoate) is involved with two reactions: complexation of the Technetium Tc 99m metal with the ligand and conjugation to Nofetumomab.

The stannous gluconate complex (Container 4) performs two functions. The stannous ion reduces the oxidation state of Technetium Tc 99m. The gluconate acts as an intermediate transfer agent to stabilize the reduced Technetium Tc 99m prior to chelation to the phenthioate ligand.

The glacial acetic acid: 0.2 N hydrochloric acid (Container 3) is used to adjust the pH to induce the transchelation reaction (transfer of reduced Technetium Tc 99m from gluconate to phenthioate).

The sodium bicarbonate buffer (Container 6) is used to adjust the Technetium Tc 99m-phenthioate ligand (active ester) reaction mixture to pH 10. The basic pH deprotonates the epsilon amino groups of the available lysine residues on Nofetumomab. The neutral amino group can then react with the active ester to form the covalent amide bond, resulting in the formation of Technetium Tc 99m Nofetumomab Merpentan.

The anion exchange column with sterile filter (Container 8) is used to retain non-protein bound radioactive species and acts to neutralize the pH. The purified diagnostic imaging agent Technetium Tc 99m Nofetumomab Merpentan is eluted from the column into the elution vial (Container 9).

The final compounded product contains 5 - 10mg of Technetium Tc 99m Nofetumomab Merpentan radiolabeled with 555-1110 MBq (15 - 30mCi) of Technetium Tc 99m diluted with 0.9% Sodium Chloride Injection, in a final volume of 15 - 20mL. The final pH for administration is 7.25 ± 0.75. The radiochemical purity must be determined as described in the instructions and must be ≥85% for patient administration.

Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies is listed in Table 1.[1]

TABLE 1. PRINCIPAL RADIATION EMISSION DATA

Radiation	Mean % Disintegration	Mean Energy (KeV)
Gamma-2	89.07	140.5

External Radiation

The specific gamma ray constant for Technetium Tc 99m is 5.4 microcoulombs/kg-MBq-hr(0.78R/mCi-hr) at 1 cm. The first half value thickness of lead for Technetium Tc 99m is 0.017cm. A

range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of lead is shown in Table 2. To facilitate control of the radiation exposure from Megabequerel/millicurie amounts of this radionuclide, the use of a 0.25cm thickness of lead will attenuate the radiation emitted by a factor of about 1,000.

Table 2. RADIATION ATTENUATION BY LEAD SHIELDING

Lead Shield Thickness (cm)	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

To allow correction for physical decay of Technetium Tc 99m, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

TABLE 3. PHYSICAL DECAY CHART FOR TECHNETIUM Tc 99m, HALF-LIFE 6.02 HOURS

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.00	8	0.40
1	0.89	9	0.36
2	0.79	10	0.32
3	0.71	11	0.28
4	0.63	12	0.25
5	0.56	18	0.13
6	0.50	24	0.06
7	0.45		

*Calibration Time

CLINICAL PHARMACOLOGY

General

The product contains Nofetumomab, a Fab fragment of a murine monoclonal antibody NR-LU-10, that recognizes an approximately 40 kD glycoprotein antigen (carcinoma associated antigen) expressed on a variety of cancers and some normal tissues[2]. Due either to lack of antigen expression or other unknown factors, neither all patients with small cell lung cancer, nor all malignant lesions will be imaged by this agent. While the overall percentage of antigen positive tumors is not known, immunohistological evaluation of the NR-LU-10 antibody on cryopreserved fresh human tumors confirms strong reactivity with three of three small cell lung cancer tumors, and three of three tumor cell lines tested. *In vitro* studies demonstrate the immunoreactivity of the Fab fragment against the 40 kD glycoprotein carcinoma associated antigen on two of two tumor cell lines tested.

Pharmacokinetics

Following intravenous injection, clearance of Technetium Tc 99m Nofetumomab Merpentan is biphasic. It has a rapid distribution phase with a mean serum half-life of 1.5 hours, and a slower elimination phase with a mean half-life of 10.5 hours. Renal clearance is the primary route of elimination, with 64% of the injected dose of Technetium Tc 99m Nofetumomab Merpentan eliminated within the first 22 hours after administration. The secondary route of elimination is through the hepatobiliary system, leading to accumulation of radioactivity in the kidney, urinary bladder, gall bladder, and intestines. *In vitro* data reveal no evidence of Technetium Tc 99m transfer to serum proteins. Based on calculations of photon flux, clearance rates for the imaging agent, and subjective clinical assessment, optimal time for imaging is 14 -17 hours after injection.

Pharmacodynamics

In the Phase 1/2 study, Technetium Tc 99m Nofetumomab Merpentan localized to primary and/or metastatic small cell[3-7] and non-small cell lung cancer[6-9], and adenocarcinomas of the breast, ovary, colorectum, and prostate. Adenocarcinomas of the kidney and pancreas were not detected. Imaging of patients revealed accumulation of radioactivity in some normal sites due to excretion (gall bladder, intestine, kidneys, urinary bladder), nonspecific vascular localization (testes, midline nasal area, liver, spleen), or specific reactivity (pituitary gland, salivary gland, thyroid) of Technetium Tc 99m Nofetumomab Merpentan. Radioactivity also may appear to accumulate in other non-tumor areas such as regions of inflammation, increased vascular pool, or recent surgical areas. The usefulness of Technetium Tc 99m Nofetumomab Merpentan for detecting metastatic disease (particularly small lesions) may be reduced in these areas, or adjacent areas of non-tumor accumulation.

Clinical Study

A multicenter, single arm, open-label, phase 3 study was conducted in patients with previously untreated, biopsy-confirmed small cell lung cancer. Eighty-nine of 96 patients enrolled in the study were considered evaluable. The 7 inevaluable patients either did not meet one or more of the eligibility criteria, or were not imaged. The primary endpoint was the accuracy of Technetium Tc 99m Nofetumomab Merpentan in staging patients with small cell lung cancer as extensive or limited stage disease. Differentiation of limited from extensive stage disease has both prognostic and therapeutic implications in this disease. The results of the masked interpretation (off-site interpretation without access to clinical or other diagnostic information) with Technetium Tc 99m Nofetumomab Merpentan images were compared with the results of an unmasked battery of other standard diagnostic evaluations (physical exam, bone scan, chest x-ray, CT examinations of head, chest, abdomen, and bone marrow aspirate and/or biopsy). Technetium Tc 99m Nofetumomab Merpentan imaging correctly staged 73 of the 89

evaluable patients for an overall accuracy of 82% (see Table 4a). The positive predictive value of Technetium Tc 99m Nofetumomab Merpentan imaging when it demonstrated extensive disease was 94% (44/47). There were 3 patients in whom Technetium Tc 99m Nofetumomab Merpentan imaging identified false positive extensive disease; the false positive sites included uptake in axillary folds in 2 patients and uptake at the site of a recent surgical procedure in one patient.

The sensitivity for detection of extensive disease with Technetium Tc 99m Nofetumomab Merpentan imaging was 77% (44/57), compared with 88% (50/57) for the battery of all standard diagnostic tests. The remaining thirteen patients were under staged by Technetium Tc 99m Nofetumomab Merpentan imaging, with 20 false negative areas for tumor involvement: CNS (n=5), liver (n=5), bone (n=4), adrenal (n=2), pancreas, pericardium, pleural mass, and bone marrow (n=1, each).

Since Technetium Tc 99m Nofetumomab Merpentan imaging is to be performed after a histologic diagnosis is established, many or most patients may have undergone preliminary staging studies, including physical examination, chest x-ray, and CT of the chest; those found to have extensive stage disease may not require further evaluation. In the phase 3 study, 75 of the 89 patients were still considered to have limited stage disease after these three staging procedures. Results of these patients are shown in Table 4b.

As an initial test, Technetium Tc 99m Nofetumomab Merpentan imaging had the highest accuracy 82% (73/89) for clinical staging of any single diagnostic test, and it had the highest sensitivity for extensive disease identifying 44 of 57 cases (see Table 5). However, Technetium Tc 99m Nofetumomab Merpentan was always the second best test for imaging of an individual organ or area. Technetium Tc 99m Nofetumomab Merpentan was relatively insensitive for detection of metastatic disease involving the brain and adrenals (see Table 6). In some patients with extensive staged disease, not all involved organs were imaged.

TABLE 4a. DIAGNOSIS BY VERLUMA™ KIT IMAGING vs. A BATTERY OF STANDARD DIAGNOSTIC EVALUATIONS IN ALL EVALUABLE PATIENTS

		Verluma™ Kit Imaging		Initial Assessment Standard Battery of Tests	
		Extensive	Limited	Extensive	Limited
Final Diagnosis	Extensive	44	13	50	7
	Limited	3	29	2	30

TABLE 4b. DIAGNOSIS BY VERLUMA™ KIT IMAGING vs. STANDARD TESTS IN PATIENTS WITHOUT EVIDENCE OF EXTENSIVE DISEASE BY PHYSICAL EXAM, CHEST X-RAY, OR CHEST CT

		Verluma™ Kit Imaging	
		Extensive	Limited
Final Diagnosis	Extensive	31	13
	Limited	3	28

TABLE 5. COMPARATIVE ACCURACY OF VERLUMA™ KIT IMAGING WITH OTHER SINGLE DIAGNOSTIC EVALUATIONS FOR STAGING

Diagnostic Evaluation	Extensive	Limited	Overall Accuracy
Verluma™ Kit Imaging	44/57	29/32	73/89 (82%)
CT Abdomen	33/57	30/32	63/89 (71%)
Bone Scan	24/57	32/32	56/89 (63%)
Bone Marrow (asp/bx)	16/57	32/32	48/89 (54%)
CT Head	12/57	32/32	44/89 (49%)
Physical Exam	8/57	31/32	39/89 (44%)
CT Chest	5/57	32/32	37/89 (42%)
Chest X-Ray	2/57	32/32	34/89 (38%)

TABLE 6. DETECTION RATE FOR VERLUMA™ KIT IMAGING BY ORGAN

Organ	Detection Rate (%)	95% CI
Lung	69/79 (87%)	78 - 94%
Neck/Axilla	20/24 (86%)	67 - 96%
Mediastinum	41/50 (82%)	69 - 91%
Bone	21/26 (81%)	61 - 93%
Bone Marrow	13/17 (76%)	50 - 93%
Liver	17/27 (63%)	42 - 81%
Pleura	8/15 (53%)	27 - 79%
Brain	3/12 (25%)	5 - 57%
Adrenal	0/9	0 - 47%
Abdominal Nodes	0/6	0 - 27%
Head	0/1	0 - 95%
Other	2/7 (29%)	4 - 71%
Total	194/274 (71%)	

INDICATIONS AND USAGE

Technetium Tc 99m Nofetumomab Merpentan is indicated for the detection of extensive stage disease in patients with biopsy-confirmed, previously untreated small cell lung cancer. Where Technetium Tc 99m Nofetumomab Merpentan imaging is interpreted as limited stage disease (limited to one hemithorax,

mediastinum, bilateral hilar lymph nodes, ipsilateral supraclavicular nodes), additional diagnostic tests should be performed to exclude extensive stage disease. Bone scan, CT examinations of head, chest, abdomen, chest x-ray, and/or bone marrow aspirate/biopsy have been shown to demonstrate additional sites of involvement in some patients.

Technetium Tc 99m Nofetumomab Merpentan imaging is not indicated for differential diagnosis of suspected lung cancer or suspected metastases. Technetium Tc 99m Nofetumomab Merpentan is intended for single use prior to treatment: it is not intended for assessment of response or evaluation following chemotherapy or radiotherapy (see Precautions).

CONTRAINDICATIONS

Technetium Tc 99m Nofetumomab Merpentan should not be used in patients who are hypersensitive to this or any other product of murine origin.

WARNINGS

Allergic reactions, including anaphylaxis, can occur in patients who receive murine antibodies. Serious allergic reactions have not been observed in clinical trials after Technetium Tc 99m Nofetumomab Merpentan administration. Appropriate medications and equipment for the treatment of hypersensitivity reactions should be available during administration of this agent.

PRECAUTIONS

General

Technetium Tc 99m Nofetumomab Merpentan may not visualize some sites of involvement by small cell lung cancer. A pattern of localization that suggests limited disease does not exclude the possibility of extensive stage disease. For those patients with evidence of limited disease by Technetium Tc 99m Nofetumomab Merpentan imaging, additional tests should be performed to confirm the absence of additional sites of disease (see Phase 3 Trial, Indications and Usage).

A negative Technetium Tc 99m Nofetumomab Merpentan scan (no tumor localization) should not alter patient management, or be used to rule out a diagnosis of small cell lung cancer since some cases of small cell lung cancer may not bear the 40kD antigen (see Phase 3 Trial).

Technetium Tc 99m Nofetumomab Merpentan may accumulate in nontumor sites such as the organs of excretion, certain normal tissues, areas of inflammation, increased blood flow, or recent surgery, and in a variety of other histologic types of cancer. Antibody images should be interpreted in the context of the known sites of inflammation or surgery by a physician experienced in the evaluation of nuclear medicine images. When clinically important, the physician should consider confirmation of areas of increased activity with use of another diagnostic procedure.

Clinical studies did not include those patients who had received prior chemotherapy or radiation therapy. Thus, safety and efficacy of Technetium Tc 99m Nofetumomab Merpentan has not been established in such patients.

There are no data to support the safety or efficacy of Technetium Tc 99m Nofetumomab Merpentan readministration. Technetium Tc 99m Nofetumomab Merpentan should be used only once in each patient.

To minimize the radiation dose to the bladder, the patient should be encouraged to drink fluids and to void as often as possible for 12-14 hours after receiving Technetium Tc 99m Nofetumomab Merpentan. Since the hepatobiliary system and gastrointestinal tract are secondary routes of excretion, use of cathartics may reduce radiation exposure. Care should be taken in patients with impaired renal or hepatobiliary function. This product has not been used in such patients.

This product should be prepared according to the product radiolabeling instructions. All kit components, containers and supplies used in the preparation of the radiolabeled Nofetumomab Merpentan are single use and must be disposed of properly. Under no circumstances is any component to be reused. **The contents of the kit are intended only for use in the preparation of Technetium Tc 99m Nofetumomab Merpentan, and individual components are NOT to be administered directly to the patient.**

At least 555 MBq (15mCi) of the final preparation should be administered to ensure that a sufficient dose is used to acquire adequate images. **Reducing the dose of Technetium Tc 99m Nofetumomab Merpentan may adversely impact imaging results, and is not recommended.**

The contents of the Verluma™ kit are not radioactive, however, after sodium pertechnetate Tc 99m is added, adequate shielding of the intermediate formulations and final preparation must be maintained. In the use of any radioactive material, care should be taken to ensure minimum radiation exposure to the patient and personnel consistent with proper patient management.

Radiopharmaceuticals should be used only under the supervision of physicians who are qualified by training and experi-ence in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

Information for Patients

Murine monoclonal antibodies are foreign proteins, and their administration can induce human anti-mouse antibodies (HAMA). While limited data exist concerning the clinical significance of HAMA, the presence of HAMA may interfere with murine antibody-based immunoassays, could compromise the efficacy of in vitro or in vivo diagnostic or therapeutic murine antibody-based agents, and may increase the risk of adverse reactions to such agents. For these reasons, patients should be

informed that the use of this product could affect the future use of other murine-based products, including Technetium Tc 99m Nofetumomab Merpentan, and should be advised to discuss prior use of murine antibody-based products with their physicians (see Heterologous Protein Administration).

Heterologous Protein Administration

Murine monoclonal antibodies are heterologous proteins, and their administration can induce HAMA. When considering the administration of Technetium Tc 99m Nofetumomab Merpentan to patients who have previously received murine antibody-based products, physicians should be aware of the potential for HAMA to increase the risk of allergic reactions and to alter clearance and biodistribution of this agent. The quality or sensitivity of the imaging study may be compromised.

Mild transient allergic reactions have occurred rarely in patients receiving this product, and mild serum sickness has been observed in patients receiving other murine monoclonal antibody products.

Drug/Laboratory Test Interactions

The presence of HAMA in serum may interfere with murine antibody-based immunoassays, such as assays for carcinoembryonic antigen and CA 125. If HAMA is known or suspected to be present, the clinical laboratory should be notified that interference may occur.

No data are available on possible drug interactions. Do not mix or administer Technetium Tc 99m Nofetumomab Merpentan with other products. Sufficient time should be allowed for clearance and radioactive decay before and after the use of this product and other products using radionuclides (see Table 3).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic or mutagenic potential of Technetium Tc 99m Nofetumomab Merpentan or to evaluate its effect on fertility in males or females.

Pregnancy Category C

Animal reproduction studies have not been conducted with Technetium Tc 99m Nofetumomab Merpentan. It is also not known whether Technetium Tc 99m Nofetumomab Merpentan can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Technetium Tc 99m Nofetumomab Merpentan should not be administered to a pregnant woman unless, in the opinion of the physician, the information to be gained outweighs the potential risks.

Nursing Mothers and/or Lactating Women

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Technetium Tc 99m Nofetumomab Merpentan is administered to a nursing woman. Formula feedings should be substituted for breast feedings for at least 60 - 72 hours following administration.

Pediatric Use

Safety and effectiveness of Technetium Tc 99m Nofetumomab Merpentan in pediatric patients have not been established.

ADVERSE REACTIONS

Among 515 patients with a variety of carcinomas who have received intravenous doses of Technetium Tc 99m Nofetumomab Merpentan, the following adverse reactions were noted: self-limited elevations in temperature (2 patients), urticaria or mild allergic reactions (3 patients).

In 53 of 89 subjects in the phase 3 trial, with both pre- and postinfusion samples, only 6% (n=3) developed elevated HAMA levels when assayed by an anti-nofetumomab ELISA. Compared to pretreatment HAMA levels, the increases in these 3 patients were 2-fold, 6-fold, and 40-fold, respectively. Analysis of subsequent serum samples in 2 of 3 patients revealed a return of HAMA levels to the normal range within 3 to 4 months. The HAMA level in the third patient (with the 40-fold increase) was declining but did not return to baseline within 4 months. In the patients with elevated HAMA, the antibodies reacted primarily with Nofetumomab and weakly with other mouse immunoglobulins. No toxicity was associated with the HAMA elevations.

Immunohistochemistry analysis demonstrated binding of NR-LU-10, the parent antibody for Nofetumomab, to normal pancreas and salivary glands. Transient changes in serum lipase or amylase have occurred in 20 patients and were not associated with any clinical symptoms. Seven patients exhibited mild elevations in amylase, ten patients experienced mild elevations in lipase levels and 3 patients experienced elevations in both enzymes.

OVERDOSAGE

The maximum amount of Technetium Tc 99m Nofetumomab Merpentan that can be safely administered has not been determined. The largest single dose administered in the clinical studies is 19.9mg of Technetium Tc 99m Nofetumomab Merpentan.

DOSAGE AND ADMINISTRATION

The recommended dose for intravenous administration in a single dose is 5 - 10mg Nofetumomab Merpentan labeled with 1,110 MBq (30mCi) Technetium Tc 99m in 15 - 20mL Sodium Chloride Injection. The dose should be administered over 3 - 5 minutes intravenously by injection from a 20mL shielded syringe. At least 555 MBq (15mCi) of the final preparation should be administered to ensure an adequate dose of radiolabeled antibody is used to obtain satisfactory images 14 - 17 hours after injection. The radiochemical yield may be variable based upon experience and training. **Reducing the dose of Technetium Tc 99m Nofetumomab Merpentan may adversely impact imaging results and is not recommended.**

The radiolabeled product may be held for up to six hours at room temperature prior to patient infusion but, at least 555MBq (15mCi) should be administered. The components contained in this kit contain no preservatives.

The patient dose should be measured by a suitable, calibrated radioactivity measurement system immediately prior to administration. Radiochemical purity must be ≥85% prior to patient administration as determined by the procedure described in the instructions.

A cathartic may be administered orally after administration of the radiolabeled Nofetumomab Merpentan at an appropriate time to be effective before initiation of imaging; this may reduce background radioactivity in the intestine. Patients should be well hydrated and should void as much as possible prior to image acquisition.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter and/or discoloration are detected in any kit component or final product, Technetium Tc 99m Nofetumomab Merpentan should not be administered and the distributor should be notified immediately.

Radiation Dosimetry

The estimated radiation dose absorbed by an average 70 kg adult after an intravenous injection of 1,110 MBq (30mCi) of Technetium Tc 99m Nofetumomab Merpentan is shown in Table 7.

TABLE 7. ESTIMATED ABSORBED RADIATION DOSE FOR A 70 kg PATIENT RECEIVING 1,110 MBq (30 mCi) TECHNETIUM Tc 99m NOFETUMOMAB MERPENTAN

	Absorbed Dose	
Tissue	rad/30 mCi	mGy/1,110MBq
Gall Bladder Wall	5.6	56
Intestine Wall (Small)	1.6	16
Intestine Wall (Lower Large)	2.0	19
Intestine Wall (Upper Large)	2.7	27
Kidney	3.9	38
Liver	1.3	13
Lungs	0.74	7.3
Ovaries	0.93	9.3
Red Marrow	0.47	4.7
Spleen	0.56	5.6
Testes	0.45	4.4
Thyroid	0.91	9.0
Uterus	0.87	8.6
Total Body	0.47	4.7

Image Acquisition and Interpretation

Data from clinical trials indicate that optimal diagnostic images are routinely obtained between 14-17 hours after injection. To obtain adequate counting statistics, a planar image of the chest should be acquired in the anterior view for 500,000 counts or

10 minutes, whichever is shorter. All subsequent images should be acquired for the same time.

Imaging with Technetium Tc 99m Nofetumomab Merpentan may show artifacts of apparent increased activity at skin folds in the area of the axilla, breast and lower abdomen, particularly in obese patients. Artifacts in the axillae may be eliminated by imaging with the arms extended overhead.

Instructions for the Preparation of Technetium Tc 99m Nofetumomab Merpentan

Note: Read complete directions thoroughly before starting preparation.

General and Procedural Precautions

1) The components should be inspected before use. Should any particulate matter, discoloration, breakage or leakage be noted, contact the distributor.
2) The components of the Verluma™ kit are sterile, non-pyrogenic, and do not contain preservatives. It is important that the user adhere to strict aseptic procedure during the preparation, withdrawal and administration of the Technetium Tc 99m Nofetumomab Merpentan. Use germicide swabs to wipe each vial prior to entry into vial.
3) All components, vials, and supplies used in the preparation of the kit must be disposed of properly. Under no circumstances is any component to be reused. Substitution of components for use with a kit of a different lot number is not recommended.
4) Proper techniques and precautions for handling radioactive materials should be employed. Waterproof gloves should be worn during the labeling procedure. Shielded syringes should be used when adding the sodium pertechnetate eluant to the reaction vial, for withdrawal of intermediate preparations, and administration of the final dose.
5) The Technetium Tc 99m labeling reactions[10] depend on maintaining the stannous ion in a reduced state. Therefore, sodium pertechnetate Tc 99m solution containing oxidants should not be used. If generator-produced Technetium Tc 99m is used, the generator must be eluted at a time that insures that 2,775 - 3,700MBq (75 - 100mCi) be obtained in a volume of 1.0mL.
6) In order to assure appropriate incubation temperatures, provide a shielded water bath at a temperature of 75°C ± 5°C and an ice-chilled shielded container before beginning the preparation of Technetium Tc 99m Nofetumomab Merpentan.
7) The radiochemical purity of Technetium Tc 99m Nofetumomab Merpentan must be checked prior to administration to the patient, according to the instructions below. If the radiochemical purity is not ≥ 85%, the product must not be administered.

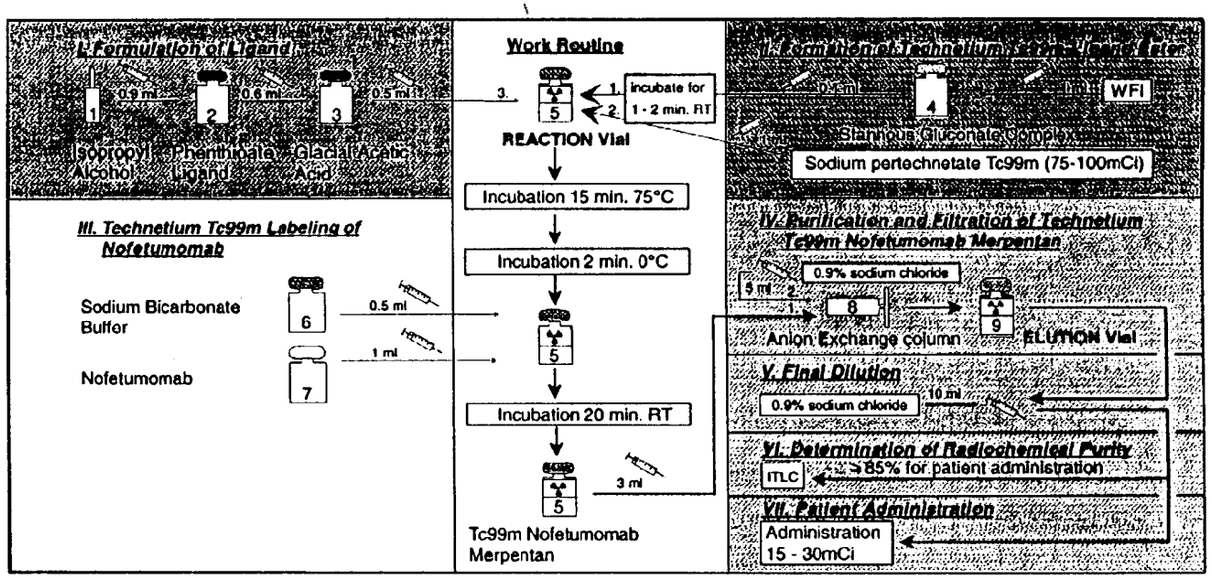
Procedure for the Preparation of Technetium Tc 99m Nofetumomab Merpentan

Note: The directions outlined below must be carefully followed for optimum preparation of the Technetium Tc 99m Nofetumomab Merpentan. The radiochemical yield may be variable based upon training and experience. A training program for preparation of Technertium Tc 99m Nofetumomab Merpentan is available from the distributor.

Required materials not supplied in the kit

1. Any commercial source of oxidant-free sodium pertechnetate Tc 99m in 0.9% sodium chloride, sterile and non-pyrogenic. Labeling requires 2,775 - 3,700 MBq (75 - 100mCi) in 1.0mL volume.
2. Sterile Water for Injection, USP, 1mL.
3. 0.9% Sodium Chloride Injection, USP, 20mL.
4. 1mL insulin syringes, sterile with permanently attached 27 - 28 gauge needles (6 each).
5. 5mL luer-lok syringe, disposable, sterile (2 each).
6. 20mL syringe, disposable, sterile (1 each).
7. 1 x 22 gauge needle, disposable, sterile (5 each).
8. 0.2 µm sterile filter.
9. Germicide to swab vial closures.
10. Lead shielded container to accommodate 10mL vial (2 each).
11. Lead shielded container to accommodate 10mL vial pre-chilled on ice (1 each).
12. Lead shielded container to accommodate 10mL vial for incubation at 75°C (1 each).
13. Timer.
14. Water bath maintained at 75°C ± 5°C.
15. Dose Calibrator.
16. Gamma counter or multichannel analyzer.
17. Ring stand to support column.
18. Adequate lead shielded work station.
19. Silica Gel Impregnated Glass Fiber Sheets as ITLC™ SG, 20 x 20 sheets, Product No. 61886 (available from Gelman Sciences, Inc., Ann Arbor, Michigan).
20. 12% (w/v) aqueous trichloroacetic acid.
21. Thin layer chromatography developing chamber.
22. Oven to activate ITLC for quality control on Technetium Tc 99m Nofetumomab Merpentan.
23. Lead shield for a 20cc syringe (available from nuclear imaging accessory suppliers).
24. Ice Bath.

Technetium Tc 99m Nofetumomab Merpentan Preparation Flow Chart



The preparation of Technetium Tc 99m Nofetumomab Merpentan consists of six process steps:

I. Formulation of Ligand
II. Formation of Technetium Tc 99m Ligand Ester
III. Technetium Tc 99m Labeling of Nofetumomab
IV. Purification and Filtration of Tc 99m Nofetumomab Merpentan
V. Final Dilution
VI. Determination of Radiochemical Purity
VII. Patient Administration

I. Formulation of Ligand

A. Swab rubber closure of the vial containing the ligand (Container 2) with germicide.
B. Using a sterile, disposable 1mL syringe, aseptically withdraw 0.9 mL of isopropyl alcohol from the freshly opened ampule (Container 1) and aseptically inject the isopropyl alcohol into the ligand vial (Container 2); keep the syringe connected to the vial.
C. Shake the ligand vial (Container 2) until the ligand is thoroughly dissolved. NOTE: This process takes approximately two minutes; complete dissolution is indicated by the disappearance of the thin film of ligand from the bottom surface of the vial (Container 2).
D. Using the attached syringe, aseptically withdraw 0.6mL of the ligand solution (Container 2).
E. Swab the rubber closure of the vial containing the glacial acetic acid: 0.2 N hydrochloric acid solution (Container 3) with germicide.
F. Aseptically inject the 0.6mL of ligand solution into the vial containing the glacial acetic acid: 0.2 N hydrochloric acid solution (Container 3); keep the syringe connected to the vial (Container 3). Gently agitate the solution.
G. Using the attached syringe, aseptically withdraw 0.5mL of the acidified ligand solution (Container 3). Cap the syringe and set it aside.

II. Formation of Technetium Tc 99m Ligand Ester

A. Swab the rubber closure of the stannous gluconate complex (Container 4) and the Sterile Water for Injection vial with germicide. Aseptically inject 1mL of Sterile Water for Injection into the stannous gluconate complex (Container 4); keep the syringe connected to the vial (Container 4). Gently agitate the vial (Container 4) until the lyophilized contents are dissolved.
B. Using the attached syringe, aseptically withdraw 0.1mL of the stannous gluconate solution (Container 4).
C. Obtain the REACTION vial (Container 5) and swab the rubber closure with germicide. Aseptically inject the 0.1mL of stannous gluconate solution into the REACTION vial (Container 5). Affix the "Caution Radioactive Material" label to the REACTION vial (Container 5) and place the vial (Container 5) into a lead shielded container.

D. Using a shielded syringe aseptically inject 75 to 100 mCi sodium pertechnetate Tc 99m solution in a volume of 1.0mL into the shielded REACTION vial (Container 5) containing 0.1mL stannous gluconate solution.

E. Gently agitate the REACTION vial (Container 5) to mix the contents.

F. Note the time and store the shielded REACTION vial (Container 5) at room temperature for at least one minute, but no longer than two minutes.

G. Immediately inject the 0.5mL acidified ligand solution (Prepared in Step I.G.) into the REACTION vial (Container 5).

H. Gently agitate the solution to ensure mixing. Place the REACTION vial (Container 5) into a shielded water bath at 75°C ± 5°C for 15 minutes.

I. Immediately transfer the heated REACTION vial (Container 5) into an ice-cold chilled lead container, or shielded ice bath for at least two minutes.

III. Technetium Tc 99m Labeling of Nofetumomab

A. Swab the rubber closure of the vial containing sodium bicarbonate buffer (Container 6) and the vial containing Nofetumomab (Container 7) with germicide.

B. Using a 1mL syringe, aseptically withdraw 0.5mL sodium bicarbonate buffer (Container 6). Replace the needle cap and set the syringe aside.

C. Using a 1mL syringe, aseptically remove 1.0mL from the vial containing Nofetumomab (Container 7). Cap the syringe and set it aside.

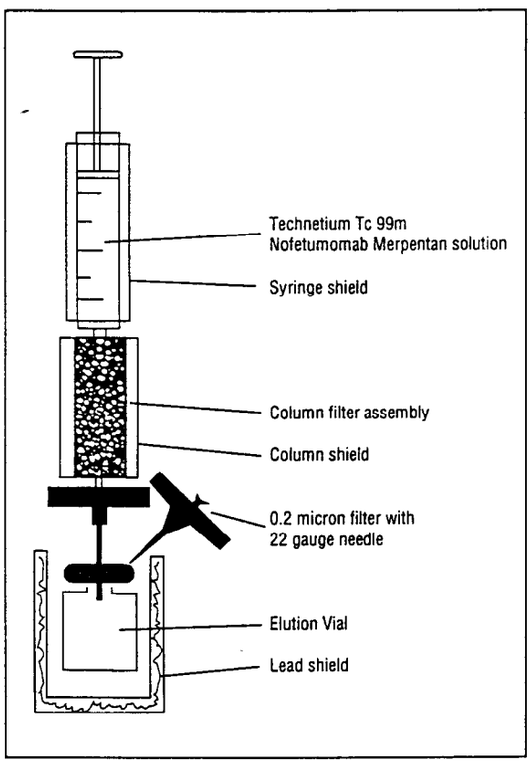
D. Remove the REACTION vial (Container 5) containing Technetium Tc 99m ligand ester solution prepared in Step II from the ice bath or chilled lead container and place the vial (Container 5) into another shielded container at room temperature.

E. Swab the rubber closure of the REACTION vial containing the Technetium Tc 99m ligand ester prepared in Step II (Container 5) with germicide. Aseptically inject the 0.5mL of bicarbonate buffer (prepared in Step III B) into the REACTION vial (Container 5). Gently agitate the shielded vial (Container 5) to ensure mixing.

F. Without delay, gently inject the Nofetumomab in the syringe prepared from Step III C into the REACTION vial (Container 5) containing the buffered Technetium Tc 99m ligand ester (avoid foaming). Gently agitate the shielded vial (Container 5) to mix the contents.

G. Incubate the radioactive reaction mixture (Container 5) in a shielded container at room temperature for 20 minutes.

IV. Purification and Filtration of Technetium Tc 99m Nofetumomab Merpentan



A. During the incubation of the Technetium Tc 99m Nofetumomab Merpentan solution (Container 5) (Step III G), aseptically prepare the following components:

1. Affix "Caution Radioactive Material" label to the ELUTION vial (Container 9).
2. Swab the rubber closure of the empty ELUTION vial (Container 9). Aseptically add a sterile disposable needle with an attached 0.2 micron filter to vent the vial (Container 9).
3. Remove the bottom cap from the anion exchange column 0.2 micron filter assembly (Container 8). Attach a sterile disposable needle with needle cap to the 0.2 micron filter assembly.
4. Remove the needle guard from the needle attached to the 0.2 micron filter of the anion exchange column and insert the needle into the ELUTION vial (Container 9).

5. Using a 5mL luer-lok syringe with a needle, aseptically withdraw 5mL of Sodium Chloride for Injection, 0.9% USP. Carefully remove any air bubbles from the syringe containing the sodium chloride solution. Replace needle guard and set the syringe aside.

B. After incubation of the Technetium Tc 99m Nofetumomab Merpentan reaction mixture (Container 5) (Step III G), measure total radioactivity of the REACTION vial (Container 5) in a dose calibrator. Subsequently aseptically withdraw the radioactive solution into a shielded 5mL luer-lok syringe. Assure that more than 90% of the radioactivity in the REACTION vial (Container 5) has been transferred to the syringe by measurement of the residual radioactivity in the empty REACTION vial (Container 5). Carefully, remove all air bubbles from the solution while bringing the solution to the top of the syringe barrel.

C. Carefully remove the needle from the syringe containing Technetium Tc 99m Nofetumomab Merpentan and the top cap from the anion exchange column (Container 8) (on the end opposite the 0.2 micron filter). Connect the shielded 5mL syringe containing Technetium Tc 99m Nofetumomab Merpentan to the shielded anion exchange column (Container 8).

D. Slowly inject the Technetium Tc 99m Nofetumomab Merpentan into the anion exchange column (Container 8) collecting the eluate into the ELUTION vial (Container 9).

E. Remove the shielded 5 mL syringe from the top of the anion exchange column (Container 8). Attach the 5mL syringe containing the 5mL of Sodium Chloride for Injection, 0.9% USP.

F. Slowly, over 2 minutes, inject the sodium chloride solution into the anion exchange column (Container 8) collecting the eluate into the same ELUTION vial (Container 9).

G. Measure total reactivity in the ELUTION vial (Container 9) using a dose calibrator.

V. Final Dilution

A. Withdraw 10mL of 0.9% Sodium Chloride for Injection into a shielded sterile, 20mL syringe and then into this syringe withdraw the entire contents of the Technetium Tc 99m Nofetumomab Merpentan vial (ELUTION vial) (Container 9). Mix the solution in the syringe. Drop an aliquot of about 50µl into an eppendorf cup for subsequent quality control by ITLC.

B. Determine the Radiochemical Purity (described below). The preparation must have a purity of 85% or greater. If the result of this test indicates a purity of less than 85% do not administer the product and contact the distributor.

VI. Determination of Radiochemical Purity

A. In order to assess Radiochemical Purity of Technetium Tc 99m Nofetumomab Merpentan, the following must be prepared and assembled in advance:

1. Thin layer chromatography developing chamber;
2. Gamma counter calibrated for Technetium Tc 99m;
3. Chromatographic Solvent: Prepare a 12% (w/v) trichloroacetic acid (TCA) in water solution. The solvent can be prepared as a stock reagent and is stable for at least 30 days when stored refrigerated.
4. Silica Gel Impregnated Glass Fiber Sheets: Pre-cut the strips to a final dimension of 2 by 10 cm. NOTE: The strips are fragile, use caution during handling. Activate the pre-cut strips according to manufacturer's instruction. Store the activated strips after activation according to manufacturer's instructions.

B. Test Procedure

1. Carefully remove an activated ITLC chromatographic strip from a storage container using forceps. Using a pencil, carefully mark the origin at approximately 1.2cm from one end of the strip.
2. Spot a small drop (2 to 5µl) of product at the origin. Allow the spot to dry prior to beginning chromatographic development.
3. Place the chromatographic strip into the developing chamber. Do not immerse the origin into the solvent.
4. Develop the chromatographic strip, allowing the solvent to ascend to about 1cm from the strip top. Remove the strip from the developing chamber and allow it to dry.
5. Cut the developed chromatographic strip into three sections. Identify the sections as origin, middle, and solvent front. Using the developing system described above, Technetium Tc 99m Nofetumomab Merpentan remains at the origin and most non-protein bound Technetium Tc 99m labeled material travels with the solvent front. The middle section of the chromatographic strip may be used to verify complete separation between product and impurities (less than 5% of total Technetium Tc 99m activity should be assayed on this section of the strip).
6. Using a suitable radioactivity counter (e.g., gamma counter), count each section of the strip. Count long enough to determine a statistically significant count for each strip section (30 sec).

Calculate the radiochemical purity (percent Technetium Tc 99m Nofetumomab Merpentan) using the following formula: (Counts Origin Area/Counts Solvent ± Counts Middle Section + Counts Origin Area) x 100%.

If the Radiochemical Purity is not ≥ 85%, do not administer the product.

VII. Patient Administration

A. Determine the amount of radioactivity in the syringe using a dose calibrator.

B. Record the amount of radioactivity in the syringe, patient i.d., volume and time and date prepared on the lead shield label. Affix the label on the lead shield and deliver product for administration.

How Supplied

Verluma™, Kit for the preparation of Technetium Tc 99m Nofetumomab Merpentan is supplied as a single use kit that contains one each of the following components in sterile, non-pyrogenic form:

Container	Contents
1	Isopropyl Alcohol, 99%, 1.5mL
2	Phenthioate Ligand (2,3,5,6-tetrafluorophenyl-4,5-bis-S-(1-ethoxyethyl)-thioacetoamidopentanoate), 0.28mg (dried)
3	Glacial Acetic Acid: 0.2 N Hydrochloric Acid 1:7 (v/v), 0.16mL
4	Stannous Gluconate Complex containing Sodium Gluconate, 45mg, and Stannous Chloride, Dihydrate, 0.79mg (lyophilized)
5	Reaction Vial - Empty, 10mL
6	1 M Sodium Bicarbonate Buffer, pH 10, 1mL
7	Nofetumomab (Fab fragment of murine monoclonal antibody NR-LU-10) in Phosphate Buffered Saline, contains 10mg in 1mL
8	Anion Exchange Column, 5mL with 0.2 µm Sterile Filter
9	Elution Vial - Empty, 10mL

In addition, the kit also contains one (1) package insert, six (6) vial lead shield labels, and six (6) radiation warning labels.

Storage

The Verluma™ kit should be stored at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. After preparation of Technetium Tc 99m Nofetumomab Merpentan, store at controlled room temperature (20°C to 25°C/68°F - 77°F). Technetium Tc 99m Nofetumomab Merpentan contains no preservatives and must be used within six hours of preparation.

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Additional Information

Verluma™ is manufactured by Dr. Karl Thomae GmbH, an affiliated company of Boehringer Ingelheim International GmbH. The NR-LU-10 imaging product was developed by NeoRx Corporation, Seattle, WA.

Distribution of the kit is by DuPont Radiopharmaceutical Division of The DuPont Merck Pharmaceutical Company. Any adverse reaction or product defect found with this product should be reported to DuPont Radiopharmaceutical Division, 1-800-362-2668.

U.S. Patent 4,897,255
U.S. Patent 5,037,630
U.S. Patent 5,120,526
U.S. Patent 5,175,343
U.S. Patent 5,242,679

Made in Germany

Thomae

Manufactured by:

Dr. Karl Thomae GmbH
an affiliated company of
Boehringer Ingelheim International GmbH
55216 Ingelheim/Germany
U.S. License No. 1199

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PHARMA

Marketed By

DuPont Radiopharmaceutical Division
The DuPont Merck Pharmaceutical Company
331 Treble Cove Road
Billerica, Massachusetts 01862

For Ordering Tel. Toll Free: 800-225-1572
All other business: 800-362-2668
(For Massachusetts and International, call 508-667-9531)

CAUTION
RADIOACTIVE
MATERIAL

CAUTION:
Federal law prohibits dispensing without prescription

Kit for the Preparation of Technetium Tc 99m
Nofetumomab Merpentan
Verluma™

mBq(mCi)

Patient I.D.

Volume mL

Time/Date Prepared

Kit Lot No

Store at room temperature

Use within six hours of preparation.
39680/USA 1a

Dr. Karl Thomae GmbH
Biberach, Germany
an affiliated company of
Boehringer Ingelheim
International GmbH

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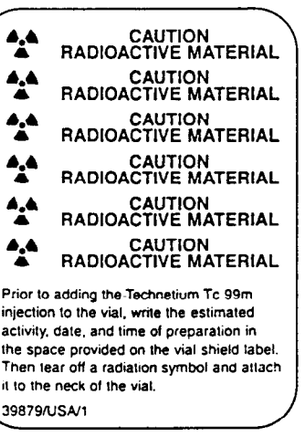
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Prior to adding the Technetium Tc 99m injection to the vial, write the estimated activity, date, and time of preparation in the space provided on the vial shield label. Then tear off a radiation symbol and attach it to the neck of the vial.
39879/USA/1