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ProstaScint™ Kit
(Capromab Pendetide)

Kit for the Preparation of Indium In 111 Capromab Pendetide
For Intravenous Use Only

DESCRIPTION

ProstaScint™ (Capromab Pendetide) is the murine monoclonal antibody, 7E11-C5.3, conjugated to the linker-chelator, glycyl-tyrosyl-(N, ε-diethylenetriaminepentaacetic acid)-lysine hydrochloride (GYK-DTPA-HCL). The 7E11-C5.3 antibody is of the IgG1, kappa subclass (IgG1K). This antibody is directed against a glycoprotein expressed by prostate epithelium known as Prostate Specific Membrane Antigen (PSMA). The PSMA epitope recognized by monoclonal antibody (MAb) 7E11-C5.3 is located in the cytoplasmic domain. Expression of this glycoprotein has not been demonstrated on any other adenocarcinomas or transitional cell cancers tested. The antibody is produced by serum-free *in vitro* cultivation of cells, and purified by sequential protein isolation and chromatographic separation procedures.

Each ProstaScint™ kit consists of two vials which contain all of the non-radioactive ingredients necessary to produce a single unit dose of Indium In 111 ProstaScint™, an immunoscintigraphic agent for administration by intravenous injection only. The ProstaScint™ vial contains 0.5 mg of capromab pendetide in 1 ml of sodium phosphate buffered saline solution adjusted to pH 6; a sterile, pyrogen-free, clear, colorless solution that may contain some translucent particles. The vial of sodium acetate buffer contains 82 mg of sodium acetate in 2 ml of Water for Injection adjusted to pH 5-7 with glacial acetic acid; it is a sterile, pyrogen-free, clear, and colorless solution. Neither solution contains a preservative. Each kit also includes one sterile 0.22 μm Millex® GV filter, prescribing information, and two identification labels.

The sodium acetate solution must be added to the sterile, non-pyrogenic high purity Indium In 111 Chloride solution to buffer it prior to radiolabeling ProstaScint™. The immunoscintigraphic agent Indium In 111 Capromab Pendetide (Indium In 111 ProstaScint™) is formed after radiolabeling with Indium In 111.

Physical Characteristics of Indium In 111

Indium In 111 decays by electron capture with a physical half-life of 67.2 hours (2.8 days).[1] The energies of the photons that are useful for detection and imaging studies are listed in TABLE 1.

<< TABLE Nº 1 >>

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External Radiation

The exposure rate constant for 37 MBq (1 mCi) of Indium In 111 is 8.3×10^{-4} C/kg/hr (3.21 R/hr). The first half-value thickness of lead (Pb) for Indium In 111 is 0.023 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of Pb is shown in TABLE 2. For example, the use of 0.834 cm of lead will decrease the external radiation exposure by a factor of about 1,000.

<< TABLE Nº 2>>

These estimates of attenuation do not take into consideration the presence of longer-lived contaminants with higher energy photons, namely Indium In 114m/114.

To allow correction for physical decay of Indium In 111, the fractions that remain at selected intervals before and after the time of calibration are shown in TABLE 3.

<< TABLE Nº 3>>

Clinical Pharmacology

Pharmacodynamics

Prostate Specific Membrane Antigen is expressed in many primary and metastatic prostate cancer lesions, and *in vitro* immunohistologic studies have shown 7E11-C5.3 to be reactive with over 95% of the prostate adenocarcinomas evaluated. In general, PSMA expression by prostate cancer cells is either unchanged or increased in patients treated with hormonal therapy (see PRECAUTIONS, Drug Interactions). The 7E11-C5.3 antibody is immunoreactive with normal and hypertrophic adult prostate tissue. In clinical studies of patients with prostate cancer, Indium In 111 ProstaScint™ localized to the prostate, and some known primary and metastatic tumor sites.

Non-antigen-dependent localization, suspected to be secondary to catabolism, has been observed in the liver, spleen, and bone marrow. Although there is variation among individuals, there may also be localization and imaging activity in the bowel, blood pool, kidneys, urinary bladder, and genitalia. Intracellular localization of 7E11-C5.3 has been observed in histochemically prepared tissue sections from normal adult skeletal and cardiac muscle, although primate studies revealed no specific localization to these tissues.

Pharmacokinetics

Based on data obtained from clinical studies, Indium In 111 ProstaScint™ demonstrated a monoexponential elimination pattern with a terminal-phase half life of 67 ± 11 hours (mean ± SD). Approximately 10% of the administered radioisotope dose is excreted in the urine during the 72 hours following intravenous infusion. The pharmacokinetics of Indium In 111 ProstaScint™ are characterized by slow serum clearance rate (42 ± 22 ml/hr) and small volume of distribution (4 ± 2.1 L).

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CLINICAL STUDIES

INDIUM IN 111 PROSTASCINT™ HAS BEEN ADMINISTERED IN SINGLE DOSES TO OVER 800 PATIENTS IN CLINICAL STUDIES, AND IN REPEAT ADMINISTRATIONS (2 TO 4 INFUSIONS) TO 81 PATIENTS. A 0.5 MG DOSE WAS DETERMINED TO BE THE LOWEST EFFECTIVE DOSE. THE IMAGING PERFORMANCE OF INDIUM IN 111 PROSTASCINT™ WAS EVALUATED IN A PHASE 2 AND A PHASE 3 TRIAL IN EACH OF TWO CLINICAL SETTINGS: (1) PATIENTS WITH CLINICALLY-LOCALIZED PROSTATE CANCER WHO WERE AT HIGH RISK FOR METASTASES AND (2) PATIENTS WITH A HIGH CLINICAL SUSPICION FOR OCCULT RECURRENT OR RESIDUAL PROSTATE CANCER.

IMAGING PERFORMANCE IN NEWLY-DIAGNOSED PATIENTS

IN ONE OF TWO OPEN LABEL, MULTI-CENTER, UNCONTROLLED PIVOTAL PHASE 3 TRIALS, 180 PATIENTS WITH A TISSUE DIAGNOSIS OF PROSTATE CANCER WHO WERE CONSIDERED AT HIGH RISK FOR LYMPH NODE METASTASES UNDERWENT INDIUM IN 111 PROSTASCINT™ IMMUNOSCINTIGRAPHY PRIOR TO SCHEDULED STAGING PELVIC LYMPHADENECTOMY. HIGH RISK WAS DEFINED AS AT LEAST ONE OF THE FOLLOWING: (1) PROSTATE SPECIFIC ANTIGEN (PSA) ≥ 10X THE UPPER LIMIT OF NORMAL & GLEASON SCORE ≥7; (2) PROSTATIC ACID PHOSPHATASE ABOVE THE UPPER LIMIT OF NORMAL; (3) EQUIVOCAL EVIDENCE OF LYMPH NODE METASTASES ON CT OR ULTRASOUND & PSA ≥8X THE UPPER LIMIT OF NORMAL; (4) GLEASON SCORE ≥8; OR (5) CLINICAL STAGE C & GLEASON SCORE ≥6. ALL PATIENTS HAD BEEN EVALUATED FOR METASTATIC DISEASE USING STANDARD NON-INVASIVE IMAGING TECHNIQUES, AND WERE CONSIDERED TO HAVE CLINICALLY-LOCALIZED PROSTATE CANCER. THE INDIUM IN 111 PROSTASCINT™ IMAGES WERE INTERPRETED ON-SITE, AND THE READER HAD ACCESS TO ALL CLINICAL DATA. THE INTERPRETATIONS WERE CORRELATED WITH THE RESULTS OF SURGICAL STAGING; HOWEVER, A CORRELATION OF SPECIFIC AREAS OF INDIUM IN 111 PROSTASCINT™ UPTAKE TO SPECIFIC SITES OF TUMOR INVOLVEMENT WAS NOT PERFORMED.

ONE HUNDRED FIFTY-TWO PATIENTS HAD AN INTERPRETABLE SCAN AND SURGICAL STAGING. FORTY SCANS WERE CLASSIFIED AS TRUE POSITIVE, 25 AS FALSE POSITIVE, 63 AS TRUE NEGATIVE, AND 24 AS FALSE NEGATIVE. THE RESULTS FOR IMMUNOSCINTIGRAPHY ARE SUMMARIZED IN TABLE 4.

<< TABLE Nº 4>>

SIXTY-FIVE PATIENTS (43%) HAD POSITIVE INDIUM IN 111 PROSTASCINT™ IMAGES FOR PELVIC LYMPH NODE METASTASES: OF THESE 38% (25 PATIENTS) DID NOT HAVE METASTATIC PROSTATE CANCER AT SURGERY. EIGHTY-SEVEN PATIENTS (57%) HAD NEGATIVE INDIUM IN 111 PROSTASCINT™ IMAGES: OF THESE 28% (24 PATIENTS) DID HAVE METASTATIC PROSTATE CANCER AT SURGERY. THE OVERALL ACCURACY OF INDIUM IN 111 PROSTASCINT™ IMMUNOSCINTIGRAPHY, AS MEASURED AGAINST PELVIC LYMPH NODE DISSECTION, WAS 68% (103/152).

A RETROSPECTIVE SUBSET ANALYSIS SUGGESTED THAT A POSITIVE INDIUM IN 111 PROSTASCINT™ SCAN IN PATIENTS WITH A GLEASON SCORE ≥7 AND A PSA ≥ 40 CONTAINED ADDITIONAL INFORMATION REGARDING THE LIKELIHOOD THAT TUMOR METASTASES WOULD BE FOUND AT THE SCHEDULED STAGING PELVIC LYMPHADENECTOMY.

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Imaging Performance in Patients with Occult Recurrent or Residual Disease

In the second open label, multi-center, uncontrolled pivotal phase 3 trial, 183 patients with a high clinical suspicion of residual or recurrent prostate cancer following radical prostatectomy were evaluated. Patients with a rising PSA, a negative bone scan, and negative or equivocal standard diagnostic techniques, (e.g. transrectal ultrasound, CT scan, or MRI) underwent Indium In 111 ProstaScint™ immunoscintigraphy prior to biopsy of the prostatic fossa. The Indium In 111 ProstaScint™ images were interpreted on-site, and the reader had access to all clinical data. The interpretations were correlated with the results of histopathologic analysis of the prostatic fossa biopsy specimens.

One hundred fifty-eight patients had an interpretable scan and prostatic fossa biopsy. Twenty-nine scans were classified as true positive, 29 as false positive, 70 as true negative, and 30 as false negative. The results are summarized in TABLE 5.

< TABLE Nº 5>>

Fifty-eight patients (37%) had positive Indium In 111 ProstaScint™ images in the prostatic fossa: Of these 50% (29 patients) did not have recurrent prostate cancer on biopsy. One hundred patients (63%) had negative Indium In 111 ProstaScint™ images: Of these 30% (30 patients) had recurrent prostate cancer on biopsy. The overall accuracy of Indium In 111 ProstaScint™ immunoscintigraphy, as measured against prostatic fossa biopsy, was 63% (99/158).

Indium In 111 ProstaScint™ localized to only the prostatic fossa in 29 (18%) patients, to prostatic fossa and extrafossa sites in 29 (18%) patients, and to only extrafossa sites in 39 (25%) patients. The study was not designed to evaluate extrafossa sites of uptake. Three extrafossa sites of uptake were biopsied, one of which was positive for metastatic prostate cancer.

ProstaScint™ Results in Patients with Distant Metastases

Clinical trials have not specifically studied the ability of Indium In 111 ProstaScint™ to image distant (extra-pelvic) metastases, and a limited number of patients with distant (primarily bone) metastases were enrolled. Thirteen patients out of 16 (81%) with CT evidence of distant soft tissue disease had positive extrafossa Indium In 111 ProstaScint™ scans. Thirty-five out of 61 patients (57%) with bone scan evidence of disease had positive Indium In 111 ProstaScint™ skeletal uptake; however, Indium In 111 ProstaScint™ imaging did not identify most sites of abnormal bone uptake on bone scan, nor did it demonstrate any new sites of metastasis that were not seen on bone scan. The Indium In 111 ProstaScint™ scan did, however, demonstrate sites of bone marrow metastases that were not seen on bone scan in 2 of 43 patients in the phase 1 study.

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Repeat Scans

Sixty-one patients received a total of 74 repeat infusions of Indium In 111 ProstaScint™. The incidence of adverse reactions upon repeat infusion (5%) was comparable to that observed after single infusion (4 %). Human anti-mouse antibody (HAMA) levels were detected (at levels >8ng/mL) by radioimmune assay (RIA) after single infusion in 8% (20/239) of patients while 1% of patients had levels greater than 100 ng/mL. Serum HAMA levels were detected by RIA after repeat infusion in 19% (5/27) of patients.

Biodistribution was unaltered on 65 of 70 (93%) evaluable repeat scans. The efficacy of repeat Indium In 111 ProstaScint™ imaging was not evaluated.

INDICATIONS AND USAGE

Indium In 111 ProstaScint™ is indicated as a diagnostic imaging agent in newly-diagnosed patients with biopsy-proven prostate cancer, thought to be clinically-localized after standard diagnostic evaluation (e.g. chest x-ray, bone scan, CT scan, or MRI), who are at high-risk for pelvic lymph node metastases (see CLINICAL PHARMACOLOGY, Imaging Performance in Newly-Diagnosed Patients). It is not indicated in patients who are not at high risk.

Indium In 111 ProstaScint™ is also indicated as a diagnostic imaging agent in post-prostatectomy patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease. The imaging performance of Indium In 111 ProstaScint™ following radiation therapy has not been studied.

The information provided by Indium In 111 ProstaScint™ imaging should be considered in conjunction with other diagnostic information. Scans that are positive for metastatic disease should be confirmed histologically in patients who are otherwise candidates for surgery or radiation therapy unless medically contraindicated. Scans that are negative for metastatic disease should not be used in lieu of histological confirmation.

ProstaScint™ is not indicated as a screening tool for carcinoma of the prostate nor for readministration for the purpose of assessment of response to treatment.

CONTRAINDICATIONS

Indium In 111 ProstaScint™ should not be used in patients who are hypersensitive to this or any other product of murine origin or to Indium In 111 chloride.

WARNINGS

Patient management should not be based on Indium In 111 ProstaScint™ scan results

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without appropriate confirmatory studies since in the pivotal trials, there was a high rate of false positive and false negative image interpretations (See PRECAUTIONS).

Indium In 111 ProstaScint™ images should be interpreted only by physicians who have had specific training in Indium In 111 ProstaScint™ image interpretation (see PRECAUTIONS, Imaging Precautions).

Allergic reactions, including anaphylaxis, can occur in patients who receive murine antibodies. Although serious reactions of this type have not been observed in clinical trials after Indium In 111 ProstaScint™ administration, medications for the treatment of hypersensitivity reactions should be available during administration of this agent.

Indium In 111 ProstaScint™ may induce human anti-mouse antibodies which may interfere with some immunoassays, including those used to assay PSA and digoxin (see PRECAUTIONS, Drug/Laboratory Test Interactions).

PRECAUTIONS

General

There were high rates of false positive and false negative image interpretations in the pivotal trials (see Clinical Studies). False positive scan interpretations may result in: (1) inappropriate surgical intervention to confirm scan results; (2) inappropriate denial of curative therapy if results are not confirmed; or (3) inadequate surgical staging if only areas of uptake are sampled. Surgical sampling should not be limited to the areas of positive uptake, unless histologic examination of these areas is diagnostic. Due to the potential for false negative scan interpretations, negative images should not be used in lieu of histologic confirmation. Proper patient preparation is mandatory to obtain optimal images for interpretation (see Imaging Precautions, below).

Bone scans are more sensitive than ProstaScint™ for the detection of metastases to bone, and Indium In 111 ProstaScint™ should not replace bone scan for the evaluation of skeletal metastases.

Imaging Precautions

Radiopharmaceuticals should be used only by physicians and other professionals who are qualified by training and experience in the safe use and handling of radionuclides. Indium In 111 ProstaScint™ images should be interpreted only by physicians who have had specific training in the interpretation of Indium In 111 ProstaScint™ images.

There may be Indium In 111 ProstaScint™ clearance and imaging localization observed in the bowel, blood pool, kidneys, and urinary bladder. When obtaining all 72-120 hour planar and Single-Photon Emission Computed Tomography (SPECT) images, the bladder should be catheterized and irrigated. The administration of a cathartic is required the evening before imaging the patient, and a cleansing enema should be administered within an hour prior to each 72-120 hour imaging session.

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The contents of the kit are not radioactive. However, after the Indium In 111 Chloride is added, appropriate shielding of Indium In 111 ProstaScint™ must be maintained. Care should be taken to minimize radiation exposure to patients and medical personnel, consistent with proper hospital and patient management procedures.

Each ProstaScint™ kit is a unit of use package. The contents of the kit are to be used only to prepare Indium In 111 ProstaScint™; unlabeled ProstaScint™ should NOT be administered directly to the patient. After radiolabeling with Indium In 111, the entire Indium In 111 ProstaScint™ dose must be administered to the patient for whom it was prescribed. Reducing the dose of Indium In 111, unlabeled ProstaScint™, or Indium In 111 ProstaScint™ may adversely impact imaging results and is not recommended.

The components of the kit are sterile and pyrogen-free and contain no preservative. Indium In 111 ProstaScint™ should be used within 8 hours after radiolabeling. It is essential to follow the directions for preparation carefully and to adhere to strict aseptic procedures during preparation of the radiolabeled product.

Information for Patients

Murine monoclonal antibodies (MABs) are foreign proteins, and their administration can induce HAMA. While limited data exist concerning the clinical significance of HAMA, the presence of HAMA may interfere with murine-antibody based immunoassays, or could compromise the efficacy of diagnostic or therapeutic murine antibody-based agents and increase the risk of adverse reactions. For these reasons, patients should be informed that the use of this product could adversely affect the future ability to diagnose recurrence of their tumor, the ability to perform certain other laboratory tests, or to use other murine-based products. Patients should be advised to discuss prior use of murine-antibody based products with their physicians (see Heterologous Protein Administration, below).

Heterologous Protein Administration

Indium In 111 ProstaScint™ has been shown to induce HAMA to murine IgG infrequently and with low peak levels after single administration. HAMA levels were detected (at >8 ng/mL) by RIA after single infusion in 8% (20/239) of patients, while 1% of patients had levels greater than 100 ng/mL. In addition, serum HAMA levels were detected by RIA after repeat infusion in 19% (5/27) of the patients.

While limited data exist concerning the clinical significance of HAMA, detectable serum levels can alter the clearance and tissue biodistribution of MABs. The development of persistently elevated serum HAMA levels could compromise the efficacy of diagnostic or therapeutic murine antibody-based agents. In repeat administration trials, 93% (65/70) of the evaluable repeat infusions were associated with normal tissue distribution of the MAb conjugate. Pre-infusion serum HAMA levels were generally not predictive of altered distribution.

When considering the administration of Indium In 111 ProstaScint™ to patients who have previously received other murine antibody-based products, physicians should be aware

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of the potential for assay interference and increased clearance and altered biodistribution, which may interfere with the quality or sensitivity of the imaging study. Prior to administration of murine antibodies, including Indium In 111 ProstaScint™, the physician should review the patient history to determine whether the patient has previously received such products.

Drug Interactions

The effect of surgical and/or medical androgen ablation on the imaging performance of Indium In 111 ProstaScint™ has not been studied. Preliminary data suggest hormone ablation may increase PSMA expression, with concurrent decrease in tumor expression of PSA.[3] The use of ProstaScint™ in this patient population cannot be recommended at this time.

Drug/Laboratory Test Interactions

The presence of HAMA in serum as a result of ProstaScint™ may interfere with some antibody-based immunoassays (such as PSA and digoxin). When present, this interference generally results in falsely high values. When following PSA levels, assay methods resistant to HAMA interference should be utilized. PSA assays which were found to be resistant to HAMA interference were Hybritech Tandem-R and Abbott IMX.

When patients have received Indium In 111 ProstaScint™, the clinical laboratory should be notified to take appropriate measures to avoid interference by HAMA with clinical laboratory testing procedures. These methods include the use of non-murine-based immunoassays, HAMA removal by adsorption, or sample pre-treatment to block HAMA activity.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic or mutagenic potential of Indium In 111 ProstaScint™ or to evaluate its effect on fertility.

Pregnancy

ProstaScint™ is not indicated for use in women.

Nursing Mothers and/or Lactating Women

ProstaScint™ is not indicated for use in women.

Pediatric Use

The safety and effectiveness of Indium In 111 ProstaScint™ in pediatric patients have not been established. ProstaScint™ is not indicated for use in children.

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ADVERSE REACTIONS

ProstaScint™ was generally well tolerated in the clinical trials. After administration of 529 single doses of Indium In 111 ProstaScint™, adverse reactions were observed in 4% of patients. The most commonly reported adverse reactions were increases in bilirubin, hypotension, and hypertension, which occurred in 1% of patients. Elevated liver enzymes and injection site reactions occurred in slightly less than 1% of patients. Other adverse reactions, listed in order of decreasing frequency, were: pruritus, fever, rash, headache, myalgia, asthenia, burning sensation in thigh, shortness of breath, and alteration of taste. Most adverse reactions were mild and readily reversible. Data from repeat administration in 61 patients revealed a similar incidence of adverse reactions (5%). No deaths were attributable to Indium In 111 ProstaScint™ administration.

OVERDOSAGE

The maximum amount of Indium In 111 ProstaScint™ that can be safely administered has not been determined. In clinical studies, single doses of 10 mg of Indium In 111 ProstaScint™ were administered to 20 patients with prostate cancer; the type and frequency of adverse reactions at this dose were similar to those observed with lower doses. The maximum Indium In 111 dose administered with ProstaScint™ in a clinical study was 6.5 mCi.

DOSAGE AND ADMINISTRATION

The patient dose of the radiolabel must be measured in a dose calibrator prior to administration.

The recommended dose of ProstaScint™ is 0.5 mg radiolabeled with 5 mCi of Indium In 111 chloride. Each dose is administered intravenously over 5 minutes and should not be mixed with any other medication during its administration. Indium In 111 ProstaScint™ may be readministered following infiltration or a technically inadequate scan; however, it is not indicated for readministration for the purpose of assessment of response to treatment (see INDICATIONS AND USAGE).

Each ProstaScint™ kit is a unit dose package. After radiolabeling with Indium In 111, the entire Indium In 111 ProstaScint™ dose should be administered to the patient. Reducing the dose of Indium In 111, unlabeled ProstaScint™, or Indium In 111 ProstaScint™ may adversely impact imaging results and is, therefore, not recommended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Radiation Dosimetry

The estimated absorbed radiation doses to an average adult patient from an intravenous injection of ProstaScint™ labeled with 5 mCi of Indium In 111 are shown in TABLE 6. Total dose estimates include absorbed radiation doses from both Indium In 111 and the

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INDIUM IN 114M RADIOCONTAMINANT. A LEVEL OF 0.06% OF INDIUM IN 114M WAS UTILIZED FOR THE DOSE ESTIMATES PRESENTED IN TABLE 6.

<· TABLE Nº 6>>

DIRECTIONS FOR RADIOLABELING PROSTASCINT™ WITH INDIUM IN 111 CHLORIDE

PROPER ASEPTIC TECHNIQUES AND PRECAUTIONS FOR HANDLING RADIOACTIVE MATERIALS SHOULD BE EMPLOYED. WATERPROOF GLOVES SHOULD BE WORN DURING THE RADIOLABELING PROCEDURE. THE PREPARATION OF THE PRODUCT SHOULD BE DONE BY THE FOLLOWING PROCEDURE.

..... 1. REQUIRED MATERIALS, NOT SUPPLIED:

A. INDIUM IN 111 CHLORIDE FROM AMERSHAM, INC. OR MALLINCKRODT, INC.
B. ONE STERILE 1 ML SYRINGE
C. VIAL SHIELD
D. DOSE CALIBRATOR SET FOR INDIUM IN 111
E. GELMAN ITLC-GC STRIPS
F. DEVELOPING CHAMBER FOR CHROMATOGRAPHY (E.G. SCINTILLATION VIAL)
G. 21-23 GAUGE STERILE NEEDLES
H. SHIELD FOR 10 ML SYRINGE
I. WATERPROOF GLOVES
J. ALCOHOL WIPE
K. WATER-SOLUBLE MARKER
L. 0.9% SODIUM CHLORIDE SOLUTION
M. DTPA (0.05 M SOLUTION OF DIETHYLENETRIAMINE PENTAACETIC ACID)
N. GAMMA RAY DETECTOR

..... 2. STERILE, PYROGEN-FREE INDIUM IN 111 CHLORIDE SOLUTION MUST BE UTILIZED IN THE PREPARATION OF THE INDIUM IN 111 PROSTASCINT™. THE USE OF HIGH PURITY INDIUM IN 111 CHLORIDE MANUFACTURED BY AMERSHAM, INC. OR BY MALLINCKRODT, INC. IS REQUIRED. THE INDIUM IN 111 CHLORIDE SHOULD BE USED ONLY TO RADIOLABEL THE PROSTASCINT™ AND SHOULD NOT BE INJECTED DIRECTLY INTO THE PATIENT. THE INDIUM IN 111 CHLORIDE SHOULD NOT BE UTILIZED AFTER ITS EXPIRATION DATE.

..... 3. BEFORE RADIOLABELING BRING THE REFRIGERATED PROSTASCINT™ TO ROOM TEMPERATURE. NOTE: PROSTASCINT™ IS A PROTEIN SOLUTION WHICH MAY DEVELOP TRANSLUCENT PARTICULATES. THESE PARTICULATES WILL BE REMOVED BY FILTRATION.

..... 4. CLEAN THE RUBBER STOPPER OF EACH VIAL WITH AN ALCOHOL WIPE. WITH A STERILE 1 ML SYRINGE ADD 0.1 ML OF SODIUM ACETATE SOLUTION TO THE SHIELDED VIAL OF INDIUM IN 111 CHLORIDE AND MIX. RETAIN REMAINING SODIUM ACETATE FOR USE IN STEP 7.

..... 5. WITH THE SAME 1 ML SYRINGE, WITHDRAW BETWEEN 6 & 7 MCI OF THE BUFFERED INDIUM IN 111 CHLORIDE AND ADD TO THE PROSTASCINT™ VIAL. FLUSH THE SYRINGE TO MIX THE PREPARATION. TO NORMALIZE PRESSURE, WITHDRAW AN EQUAL VOLUME OF AIR. SWIRL GENTLY TO MIX, AND ASSAY CONTENTS IN A DOSE CALIBRATOR. ON ONE OF THE LABELS PROVIDED, RECORD THE PATIENT'S IDENTIFICATION, THE DATE, TIME OF PREPARATION, AND ACTIVITY IN THE VIAL. AFFIX THE LABEL TO THE VIAL SHIELD.

..... 6. ALLOW THE LABELING REACTION TO PROCEED AT ROOM TEMPERATURE FOR 30 MINUTES.

..... 7. WITH A SYRINGE, ADD THE REMAINING SODIUM ACETATE TO THE PROSTASCINT™ REACTION VIAL. TO NORMALIZE PRESSURE, WITHDRAW AN EQUAL VOLUME OF AIR.

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..... 8. Aseptically attach the 0.22 µm Millex® GV sterile filter (provided) and a sterile hypodermic needle to a 10 mL sterile disposable syringe and withdraw the contents of the reaction vial through the filter into the syringe. Keep the needle immersed in the solution to avoid creating an air-lock in the filter.

..... 9. Remove the filter and needle. Aseptically attach a fresh sterile hypodermic needle to the syringe. Assay syringe and contents in a dose calibrator. The syringe should contain not less than 4 mCi (148 MBq) of Indium In-111.

..... 10. Radiochemical purity (RCP) by Instant Thin Layer Chromatography (ITLC) can be determined by the following procedure:

A. Mix equal parts (several drops of each) of Indium In 111 ProstaScint™ with DTPA solution. Allow the mixture to stand at room temperature for one minute. Spot a small drop of the mixture onto an ITLC strip at its origin.

B. Place the strip in a chromatography chamber with the origin at the bottom and allow the solvent to migrate 6 cm from the origin of the strip. Remove and cut the strip in half and measure the counts per minute (CPM) of both halves with a gamma ray detector.

C. Calculate the percent RCP as follows:

$$\%RCP = \frac{\text{CPM bottom half}}{\text{CPM bottom half} + \text{CPM top half}} \times 100$$

D. If the radochemical purity is <90%, the ITLC procedure should be repeated. If repeat testing remains <90%, the preparation should not be administered.

..... 11. On the second label provided in the kit, record the patient's identification, the date, time of assay, and activity in the syringe. Affix this label to the syringe shield.

..... 12. Indium In 111 ProstaScint™ should be used within 8 hours of radiolabeling.

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

Image Acquisition and Interpretation

Images should be acquired using a large field of view gamma camera equipped with a parallel hole medium energy collimator. The gamma camera should be calibrated using the 172 and 247 keV photopeaks for Indium In 111 with a 20% symmetric window.

Whole body or spot planar views of the pelvis, abdomen, and thorax should be performed between 72 and 120 hours following Indium In 111 ProstaScint™ infusion. A cathartic is required the evening before imaging and a cleansing enema should be administered within an hour prior to each 72-120 hour imaging session. In addition, the bladder should be catheterized and irrigated.

Whole body acquisition should be carried out from skull through mid-femur. The total scan time over this area should be no less than 35 minutes using a 128x512 or 256x1024 matrix.

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Planar images should be acquired in anterior and posterior views for 7.5 minutes per view using a 128x128 or 256x256 matrix. Due to uptake of Indium In 111 ProstaScint™ by the liver, planar images obtained with the liver in the field of view must be acquired with adequate counts to allow the detection of lesions in the adjacent extrahepatic abdomen and pelvis. This may result in pixel overflow with image degradation in the region of the liver.

Two SPECT imaging sessions are necessary. The first SPECT session should be of the pelvis and be performed approximately 30 minutes after infusion to obtain a blood pool image. The second SPECT session should include both the pelvis and abdomen, including the lower liver margin through the prostatic fossa and be performed between 72 and 120 hours after infusion for detection of benign and malignant prostate tissue sites. Depending upon the capability of the camera field of view to include both pelvis and abdomen, either one or two separate acquisitions may be necessary during the second session.

To resolve imaging ambiguities possibly resulting from activity in blood pool, stool or urinary bladder, follow-up imaging sessions with full patient preparation should be performed.

The SPECT images should be acquired using a 64x64 or 128x128 matrix for a minimum of 60 or 120 stops, respectively, over 360 degrees rotation for approximately 25 seconds per view at the first session and 50 seconds per view at the second session. Reconstruction should be performed using a Butterworth filter or equivalent in the transverse, coronal and sagittal views. An order of 5 and cut off of 0.5 may be used as a starting point. Slice thickness should be in the range of 6 to 12 mm.

Following Indium In 111 ProstaScint™ administration, some of the radiolabel localizes in normal liver, spleen, bone marrow and genitalia.

It has been reported that Indium In 111 labeled antibodies may localize non-specifically in colostomy sites, degenerative joint disease, abdominal aneurysms, post-operative bowel adhesions, and local inflammatory lesions, including those typically associated with inflammatory bowel disease or secondary to surgery or radiation. Indium In 111 ProstaScint™ can demonstrate apparent localization to sites of tortuous blood vessels. Careful review of the patient's medical history and other diagnostic information should aid in the interpretation of the images.

The diagnostic images acquired with Indium In 111 ProstaScint™ should be interpreted in conjunction with other appropriate diagnostic tests.

HOW SUPPLIED

The ProstaScint™ kit (NDC No. 57902-817-01) for the preparation of Indium In 111 labeled Capromab Pendetide includes one vial containing 0.5 mg of ProstaScint™ per 1 ml of sodium phosphate buffered saline and one 2 ml vial of sodium acetate solution, 0.5 M. These solutions are sterile and pyrogen free and contain no preservatives. Each

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KIT ALSO INCLUDES ONE STERILE 0.22 μM MILLEX® GV FILTER, PRESCRIBING INFORMATION, AND TWO IDENTIFICATION LABELS.

STORAGE

STORE AT 2° TO 8°C (36° TO 46°F). DO NOT FREEZE. STORE UPRIGHT.

REFERENCES

1. KOCHER, DC: RADIOACTIVE DECAY DATA TABLES. DOE/TIC 115:11026, 1981.

2. DATA SUPPLIED BY OAK RIDGE ASSOCIATED UNIVERSITIES. RADIOPHARMACEUTICAL INTERNAL DOSE INFORMATION CENTER, 1984.

3. WRIGHT, GL, JR; ET AL. EXPRESSION OF PROSTATE-SPECIFIC MEMBRANE ANTIGEN IN NORMAL, BENIGN, AND MALIGNANT PROSTATE TISSUES. UROL ONCOL. 1995: 1:18-28.

PROSTASCINT™ (CAPROMAB PENDETIDE) IS COVERED IN WHOLE OR IN PART BY AT LEAST THE FOLLOWING US PATENTS: #4,671,958, #4,741,900, AND #5,162,504.

MANUFACTURED AND DISTRIBUTED BY:
CYTOGEN CORPORATION
PRINCETON, NJ 08540-5308

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TABLES#

TABLE 1 - INDIUM IN 111 PRINCIPAL RADIATION EMISSION DATA[1]

RADIATION	MEAN % PER DISINTEGRATION	MEAN ENERGY (KEV)
GAMMA 2	90.2	171.3
GAMMA 3	94	245.4

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TABLE 2 - INDIUM IN 111 RADIATION ATTENUATION OF LEAD SHIELDING[2]

SHIELD THICKNESS (PB) CM	ATTENUATION FACTOR
0.023	0.5
0.203	10^{-1}
0.513	10^{-2}
0.834	10^{-3}
1.120	10^{-4}

TO BE INSERTED INTO THE TEXT AT THE MARKED LOCATIONS.

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TABLE 3 - INDIUM IN 111 PHYSICAL DECAY CHART, HALF-LIFE 67.2 HOURS (2.8 DAYS)

HOURS	FRACTION REMAINING
-48	1.64
-36	1.44
-24	1.28
-12	1.13
0*	1.00
12	0.88
24	0.78
36	0.69
48	0.61
60	0.54
72	0.48
84	0.42
96	0.37
108	0.33
120	0.29
132	0.26
144	0.23

* CALIBRATION TIME

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TABLE 4 - COMPARISON OF INDIUM IN 111 PROSTASCINT™ AND HISTOPATHOLOGIC RESULTS FOR PRESURGICAL PATIENTS

	Number of Patients		
	Indium In 111 ProstaScint™		
	+	−	
Biopsy +	40	24	*Sensitivity* 62%
Biopsy −	25	63	*Specificity* 72%
	Positive Predictive Value 62%	*Negative Predictive Value* 72%	*Overall Accuracy* 68%

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TABLE 5 - INDIUM IN 111 PROSTASCINT™ AND HISTOPATHOLOGIC RESULTS FOR RECURRENT OR RESIDUAL DISEASE PATIENTS

	Number of Patients		
	Indium In 111 ProstaScint™		
	+	−	
Biopsy +	29	30	*Sensitivity* 49%
Biopsy −	29	70	*Specificity* 71%
	Positive Predictive Value 50%	*Negative Predictive Value* 70%	*Overall Accuracy* 63%

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TABLE 6 - ESTIMATED AVERAGE ABSORBED RADIATION DOSE IN ADULT PATIENTS FROM INTRAVENOUS ADMINISTRATION OF PROSTASCINT® LABELED WITH 5 MCI (185 MBQ) OF INDIUM IN 111 CHLORIDE

ORGAN	AVERAGE DOSE (RAD/5 MCI)	AVERAGE DOSE (MGY/ 185MBQ)
TOTAL BODY	2.7	27
BRAIN	1.1	11
LIVER	18.5	185
SPLEEN	16.3	163
KIDNEYS	12.4	124
LUNGS	5.6	56
HEART WALL	7.8	78
RED MARROW	4.3	43
ADRENALS	5.2	52
URINE BLADDER WALL	2.2	22
BONE SURFACES	4.0	40
STOMACH	3.1	31
GALL BLADDER WALL	7.3	73
SMALL INTESTINE	3.3	33
UPPER LARGE INTESTINE WALL	5.0	50
LOWER LARGE INTESTINE WALL	7.6	76
PANCREAS	5.1	51
SKIN	1.1	11
TESTES	5.6	56
PROSTATE	8.2	82
THYMUS	2.6	26
THYROID	1.4	14
OTHER TISSUES	2.0	20

*BASED ON DATA FROM 21 PATIENTS WHO RECEIVED DOSES OF PROSTASCINT® LABELED WITH A MEAN (± SD) INDIUM IN 111 DOSE OF 4.6 ± 1.0 MCI.