MYOSCINT®
Imciromab Pentetate

Kit for the Preparation of Indium In 111 Imciromab Pentetate
Sterile, Non-Pyrogenic Solution For Intravenous Use Only

DESCRIPTION

MYOSCINT® (Imciromab Pentetate) is the Fab fragment of a murine monoclonal antibody that is bound to diethylenetriaminepentaacetic acid (DTPA). The murine antibody binds to the heavy chain of human myosin, an intracellular protein found in both cardiac and skeletal muscle cells. Imciromab is the Fab fragment of a purified immunoglobulin ($IgG2a_\kappa$) produced by cell culture. Gentamicin, at a concentration of 50 µg/mL, is used in the medium for cell culture production. The amount of gentamicin in Imciromab Pentetate is reduced to less than 0.5 µg/dose by the purification process. Imciromab is prepared by enzymatic cleavage of the whole antibody. DTPA is covalently bound to Imciromab, permitting radiolabeling of the conjugate with Indium In 111 using Indium In 111 Chloride (see Preparation for Use).

The MYOSCINT kit comprises two vials, each containing a sterile, non-pyrogenic, clear, colorless solution. The MYOSCINT vial contains 0.5 mg of Imciromab Pentetate in 1.0 mL of 10 mM sodium phosphate buffer, 145 mM sodium chloride, and 10% (w/v) maltose (pH 6.5) with no preservatives. One (1.0) mL of the solution from the MYOSCINT vial is to be added to the citrate buffer vial, which contains 1.0 mL of 0.2 M sodium citrate buffer solution (pH 5.0). Imciromab Pentetate is to be radiolabeled by the addition of a sterile, non-pyrogenic solution of high purity Indium In 111 Chloride (see Preparation for Use).

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 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

External Radiation

The exposure rate constant for 37MBq (1 mCi) of Indium In 111 is 8.3 x 10^{-4} Ci/kg/hr (3.21 Rad/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 Pb will decrease the external radiation exposure by a factor of about 1,000.

Table 2
INDIUM In 111 RADIATION ATTENUATION OF LEAD SHIELDING

Lead Shield Thickness (cm)	Coefficient of Attenuation
0.023	0.5
0.203	10^{-1}
0.513	10^{-2}
0.834	10^{-3}
1.120	10^{-4}

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 3
INDIUM In 111 PHYSICAL DECAY CHART, HALF-LIFE 67.2 HR (2.8 DAYS)

Hours	Fraction Remaining
-48	1.64
-42	1.54
-36	1.44
-30	1.36
-24	1.28
-18	1.20
-12	1.13
-6	1.06
0*	1.00
6	0.94
12	0.88
18	0.83
24	0.78
30	0.74
36	0.69
42	0.65
48	0.61
54	0.58
60	0.54
66	0.51
72	0.48

*Calibration time

CLINICAL PHARMACOLOGY

Pharmacokinetics

In humans, blood concentration-time curves of Indium In 111 MYOSCINT were fit to a two-compartment model. The initial (α) elimination half-life of Indium In 111 MYOSCINT radioactivity is 1.5 hours, while the slow (β) elimination half-life is 20.2 hours. At 24 hours, 19.2% of the initial radioactivity remains in the plasma, compared with 8.4% remaining at 48 hours. The elimination half-lives of Imciromab Pentetate as determined by enzyme-linked immunosorbant assay or by measuring radioactivity are not significantly different. The pharmacokinetics of Indium In 111 MYOSCINT have not been evaluated in patients with hepatic, renal, or cardiac insufficiency.

Pharmacodynamics

Intravenous administration of MYOSCINT radiolabeled with Indium In 111 Chloride, a gamma emitting radionuclide, provides a means of identifying regions of myocardial infarction (MI) using scintigraphic techniques.[2] In normal myocardium, intracellular proteins are isolated from the extravascular space by the cell membrane and are inaccessible to antibody binding. Cardiac myosin was chosen as the intracellular target for antibody localization because of its abundance in myocytes, its high molecular weight (500,000 daltons), and its low plasma solubility. Heavy chain myosin is not found free in the circulation. MYOSCINT contains the Fab fragment of the antibody rather than the whole immunoglobulin because the Fab fragment localizes to the necrotic myocardium to a greater degree and is cleared more rapidly from the circulation.

Circulating radiolabeled MYOSCINT (Imciromab Pentetate) does not have access to intracellular myosin *in situ* and does not localize in normal myocardial tissue. Animal studies have shown that, following irreversible myocyte injury, the cell membrane undergoes a loss of integrity and becomes permeable to macromolecules, allowing Indium In 111 MYOSCINT to bind to intracellular myosin.[3] Cross-reactivity studies performed *in vitro* on a broad spectrum of human tissues demonstrated that Imciromab Pentetate is highly specific for myocardial and skeletal muscle and does not cross-react with any of the other examined tissues.

In vivo, radiolabeled MYOSCINT localizes in infarcted myocardial tissue. In healthy volunteers, cardiac images did not show Indium In 111 MYOSCINT localization in the myocardium. Post-mortem evaluations of patients who died from complications of acute myocardial infarction shortly after Indium In 111 MYOSCINT imaging demonstrated localization of Indium In 111 MYOSCINT in the necrotic myocardium. The locations of the ante-mortem and post-mortem Indium In 111 MYOSCINT myocardial uptake correlated with the location of the histochemically determined myocardial infarct.

Clinical Studies

To evaluate the performance characteristics of Indium In 111 MYOSCINT, a Phase 3 clinical trial was conducted in 726 patients hospitalized with chest pain suspected to be due to myocardial infarction. This trial was a single-arm, non-randomized, multicenter study. Patients were excluded for cardiogenic shock, cardiomyopathy, myocarditis, valvular disease, left bundle branch block, equivocal electrocardiographic (ECG) findings, or a myocardial infarction or cardiac surgery within the two weeks prior to the study. Patients were to be injected with 2.0 mCi of Indium In 111 MYOSCINT over 30 to 60 seconds within 48 hours of the onset of chest pain. Planar images were to be obtained at 24 and 48 hours following the injection with the gamma camera in the anterior, left-anterior oblique and left-lateral positions.

A team of cardiologists blinded to the results of each patient's Indium In 111 MYOSCINT image, reviewed clinical, electrocardiographic, and enzymatic data and assigned one of the following four clinical diagnoses to each patient: i) definitive acute myocardial infarction (Q-wave, non-Q-wave, or indeterminate); ii) definitive unstable angina; iii) definitive chest pain of other etiology (e.g., noncardiac chest pain, stable angina, atypical angina); or iv) a nondefinitive diagnosis. A team of nuclear medicine physicians blinded to each patient's clinical history and outcome, interpreted the Indium In 111 MYOSCINT images. Image results at 48 hours were used for primary analysis. When these results were missing or technically inadequate, the image results from 24 hours were used instead.

Table 4 shows the distribution of patients by final clinical diagnosis and by final image interpretation. Overall, 555 (76%) of the 726 patients had diagnostic images. The 48-hour images were used for 534 of these patients, whereas the 24-hour images were used for 21 patients. Most of the non-diagnostic images were attributed to persistence of radioactivity in the blood ("blood pooling"), which was observed in 54% of the 678 patients with available scans at 24 hours and in 13% of the 664 patients with available images at 48 hours. For the 555 patients with diagnostic images, a median of 30 hours (minimum: 2 hours) elapsed between the onset of chest pain and the administration of Indium In 111 MYOSCINT. The mean administered dose of Indium In 111 MYOSCINT was 2.1 ± 0.2 mCi (range: 1.0-3.8mCi), and the mean percent incorporation of Indium In 111 was 96.6 ± 2.5% (range: 85.7-100%).

Table 4
DISTRIBUTION OF ALL PATIENTS BY
FINAL CLINICAL DIAGNOSIS AND BY IMAGING RESULTS

	Clinical Diagnosis				
	AMI	CP	UA	ND	Total
Imaging Results	*number of patients*				
All images	455	43	227	1	726
Non-diagnostic images*,	77	9	84	1	171
Diagnostic images	378	34	143	0	555
Positive (+) cardiac localization of Indium In 111 MYOSCINT	316	1	49	0	366
Negative (-) cardiac localization of Indium In 111 MYOSCINT	62	33	94	0	189

* AMI = definitive acute myocardial infarction; CP = definitive chest pain of other etiology; UA = definitive unstable angina pectoris; ND = nondefinitive diagnosis

† Includes images with blood pooling and those that were technically inadequate or unavailable

Table 5 summarizes selected performance characteristics of Indium In 111 MYOSCINT in the settings of acute myocardial infarction, unstable angina and chest pain of other etiologies. MYOSCINT imaging was most likely to detect myocardial infarctions correctly in patients with anterior myocardial infarctions, Q-wave myocardial infarctions, or myocardial infarctions with high peak creatine kinase (CK) levels (e.g., > 1000 U/L) or high peak CK-MB levels (e.g., > 100 U/L) (data not shown).

Table 5
PERFORMANCE CHARACTERISTICS OF INDIUM In 111 MYOSCINT
BASED ON FINAL CLINICAL DIAGNOSIS AND FINAL IMAGE INTERPRETATION*

DEFINITIVE DIAGNOSIS	ESTIMATE	95% CONFIDENCE INTERVAL
Acute myocardial infarction		
Positive (+) localization of Indium In 111 MYOSCINT (sensitivity)		
• In patients with diagnostic images only	316/378 = 84%	(79%, 87%)
• In all patients imaged†	316/455 = 69%	(65%, 74%)
Chest pain of other etiology		
Negative (-) localization of Indium In 111 MYOSCINT (specificity)		
• In patients with diagnostic images only‡	33/34 = 97%	(85%, 100%)
Unstable angina		
Positive (+) localization of Indium In 111 MYOSCINT		
• In patients with diagnostic images only	49/143 = 34%	(27%, 43%)
• In all patients imaged†	49/227 = 22%	(16%, 28%)

* The data used in the calculations are from Table 4.
† "All patients imaged" includes both diagnostic images and non-diagnostic images.
‡ Nine additional patients had non-diagnostic images.

Localization of myocardial infarction: Of the 177 patients with positive diagnostic images and an acute Q-wave myocardial infarction, the site of Indium In 111 MYOSCINT localization agreed with electrocardiographic localization in 89% (95% CI: 84%, 93%) of the patients. The agreement was 97% (95% CI: 90%, 99%) for the subset of 88 patients with anterior myocardial infarctions as determined by electrocardiogram (ECG), and 84% (95% CI: 74%, 91%) for the subset of 87 patients with inferior myocardial infarctions as determined by ECG. In the 8 patients for whom myocardial infarct location was indeterminate by electrocardiography, Indium In 111 MYOSCINT showed positive localization (6 anterior and 2 lateral). For non-Q-wave myocardial infarctions, the site of Indium In 111 MYOSCINT localization agreed with electrocardiographic localization (as assessed by ST-segment alterations) in 70% of the patients (23 of 33).

Extent of myocardial infarctions: A retrospective analysis with blinded interpretation of images was performed on the subgroup of patients with positive diagnostic images and an acute myocardial infarction (i.e., excluding patients with unstable angina). Of these 316 patients, the extent of cardiac uptake (on each of the three imaging views) and follow-up clinical information were both obtained on 234 patients. In this final subgroup, patients who had uptake of Indium In 111 MYOSCINT in at least 10 of 18 cardiac segments, as compared to those with positive uptake in 1 to 9 of 18 segments, appeared to be at increased risk for subsequent cardiac death and non-fatal myocardial infarction.

Delayed Administration and Repeat Administration of Indium In 111 MYOSCINT (Imciromab Pentetate):

An additional trial was conducted to evaluate the imaging characteristics of Indium In 111 MYOSCINT when administered at longer intervals after a documented myocardial infarction, and to determine safety and efficacy of repeat administrations. In this prospective study of 185 patients, the proportion of patients with positive images following injection of Indium In 111 MYOSCINT decreased progressively from 72% when the initial injection was made within two months of the acute myocardial infarction, to 23% when the initial injection was made between eight and ten months (see Table 6). No positive images were seen in the 8 patients injected between 14 and 16 months (the last time point studied) after the myocardial infarction.

Of the 185 patients who received injections of Indium In 111 MYOSCINT, 132 (71%) received one injection, 40 (22%) received two injections, 10 (5%) received three injections, and 3 (2%) received five injections. None of the patients with evaluable samples had human anti-murine antibody (HAMA) responses following single or repeat injections.

Table 6
NUMBER (%) OF PATIENTS WITH AND WITHOUT LOCALIZATION
OF INDIUM In 111 MYOSCINT AFTER A
PRIOR Q-WAVE OR NON-Q-WAVE MYOCARDIAL INFARCTION

	Time (months) from AMI to Initial Injection of Indium In 111 MYOSCINT				
	0-2	2-4	4-6	6-8	8-10
Image Results					
Positive localization	51 (72%)	23 (70%)	9 (53%)	18 (45%)	3 (23%)
Negative localization	20 (28%)	10 (30%)	8 (47%)	22 (55%)	10 (77%)

INDICATIONS AND USAGE

Indium In 111 MYOSCINT is a cardiac imaging agent for detecting the presence and location of myocardial injury in patients with suspected myocardial infarction.

CONTRAINDICATIONS

Indium In 111 MYOSCINT should not be administered to patients who are hypersensitive to this or any other product of murine origin or to Indium In 111 Chloride.

WARNINGS

Although hypersensitivity reactions are possible whenever protein-containing products are administered to patients, such reactions have not been observed in any of the 1318 patients who received more than 1394 injections of MYOSCINT in clinical trials. Patients should be monitored closely after injection for the possibility of an adverse experience.

PRECAUTIONS

General

Radiopharmaceuticals should be prepared and administered by physicians or other health care personnel qualified for safe handling of radionuclides.

The components of MYOSCINT are sterile and non-pyrogenic. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation (see Preparation for Use).

The contents of the vials are intended only for use in the preparation of Indium In 111 MYOSCINT and should not be administered directly to patients. AFTER FORMULATION, THE ENTIRE CONTENTS OF THE CITRATE BUFFER VIAL SHOULD BE USED FOR A SINGLE PATIENT.

Before preparation, the contents of the vials are not radioactive. However, after the Indium In 111 Chloride has been added, adequate shielding of the preparation must be maintained. Appropriate safety measures should be taken to minimize radiation exposure to patients consistent with proper patient management and to minimize radiation exposure to clinical personnel.

Indium In 111 MYOSCINT should be administered within eight hours of formulation. The final radiolabeled preparation can be stored at room temperature.

Persistent Localization: In a prospective study involving 185 patients with documented myocardial infarctions, Indium In 111 MYOSCINT localized to the heart in a substantial proportion of patients, even when the injections were made months after the acute event (See CLINICAL PHARMACOLOGY, Clinical Studies). The interpretation of a positive Indium In 111 MYOSCINT image may therefore be influenced by prior Q-wave or prior non-Q-wave infarctions. Caution should be exercised when Indium In 111 MYOSCINT localization is attributed to acute events, particularly if prior infarctions or ischemic events may not have been recognized (see also PRECAUTIONS, Localization in Unstable Angina).

Localization in Unstable Angina: Caution should be exercised when Indium In 111 MYOSCINT localization is equated with myocardial infarction, particularly in patients with a prior history of unstable angina (see also PRECAUTIONS, Persistent Localization). In the prospective study of 726 hospitalized patients with suspected acute myocardial infarction, Indium In 111 MYOSCINT localized to the heart in about one-third of the patients who were ultimately diagnosed with unstable angina (see CLINICAL PHARMACOLOGY, Clinical Studies). These findings may indicate that Indium In 111 MYOSCINT sometimes localizes to ischemic, non-infarcted myocardial tissue (i.e., "false positive" localization). However, an autopsy series has demonstrated necrosis in some patients with unstable angina. Therefore, Indium In 111 MYOSCINT localization in patients with unstable angina may possibly identify areas of myocardial necrosis not detectable by other means.

Other Potential Causes for Indium In 111 MYOSCINT Uptake: Health care providers should consider potential causes other than acute myocardial infarction for positive Indium In 111 MYOSCINT images. Indium In 111 MYOSCINT uptake has been seen in certain patients with myocarditis, cardiomyopathy, transplant rejection and in patients following chemotherapy with doxorubicin.

MYOSCINT® (Imciromab Pentetate)

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. For these reasons, patients should be informed that the use of this product could affect the future use of other murine-based products, including MYOSCINT (Imciromab Pentetate), and they should be advised to discuss prior use of murine-based antibody products with their physicians (see Heterologous Protein Administration).

Heterologous Protein Administration: In Centocor-sponsored trials, 914 patients had serum samples evaluable for human antimurine antibody (HAMA) response to Indium In 111 Myoscint injection. One patient had a low-level titer HAMA response. None of the other patients had HAMA responses, including 53 patients injected up to 5 times (see CLINICAL PHARMACOLOGY, see Readministration). Patients with HAMA titers may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic murine monoclonal antibodies. Should it develop, the presence of HAMA may alter the performance characteristics of Indium In 111 MYOSCINT.

Readministration: In one study, 185 patients received a total of 257 injections from one day to 68 weeks following acute myocardial infarction. Of these, 132 patients received a single injection and 53 patients received 2-5 injections. No patient developed a HAMA response. Repeat injections in this study did not increase the likelihood of a non-diagnostic image, indicating that repeat Indium In 111 MYOSCINT studies may be performed (see CLINICAL PHARMACOLOGY). Should a HAMA response develop, however, readministration may result in altered performance characteristics or in allergic or hypersensitivity reactions (see Heterologous Protein Administration).

Of 53 patients who received multiple injections of Indium In 111 MYOSCINT (up to 5 times) 4 patients reported adverse events following repeat injection (chest pain, headache, nausea, fatigue). These events are frequent sequelae of acute ischemic heart disease and/or concurrent medications and may or may not be attributable to Indium In 111 MYOSCINT administration (see also ADVERSE REACTIONS).

Drug Interactions: Although formal drug interaction studies have not been performed, interactions between Indium In 111 MYOSCINT and drugs commonly used in unstable ischemic heart disease have not been reported. Indium In 111 MYOSCINT has been coadministered with other radiopharmaceutical agents used for cardiac imaging such as thallium-201 and technetium-99m sestamibi with no reported adverse interactions. The interaction of Indium In 111 MYOSCINT with other diagnostic or therapeutic murine monoclonal antibody products has not been studied in clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: *In vitro* and *in vivo* mutagenicity studies have not demonstrated any mutagenic effect. Studies have not been performed to evaluate the carcinogenic potential or effects on fertility in male or female animals.

Pregnancy Category C: Animal reproductive studies have not been conducted with MYOSCINT. It is also not known whether MYOSCINT can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Indium In 111 MYOSCINT should not be used during pregnancy unless the potential benefit to the patient justifies the potential risk to the fetus.

Examinations using radiopharmaceuticals in women capable of bearing children, especially those which are elective in nature, should ideally be performed during the first few days following the onset of menses (e.g., within approximately 10 days of onset).

Nursing Mothers: Formula feeding should be substituted for breast feeding if Indium In 111 MYOSCINT must be administered to the mother during lactation.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Safety data were evaluated in 1318 patients who received 1394 injections of Indium In 111 MYOSCINT in Centocor-sponsored clinical trials. No anaphylaxis or hypersensitivity reactions were reported. None of the 45 patient deaths or 150 serious adverse events were reported as definitely or probably related to Indium In 111 MYOSCINT. Only one death that occurred in a patient with a prior cardiac arrest and ventricular failure was judged to be possibly related to Indium In 111 MYOSCINT. After injection, this patient experienced hypotension (possibly related) and a cardiac arrest (probably not related) and died 10 minutes after the injection. Serious adverse events reported as possibly related were infrequent. Three of these events (delirium, confusion, and hypotension) occurred in one patient.

Among the 1318 evaluated patients, 480 patients experienced a total of 1271 adverse events. Adverse events reported in >5% of patients included chest pain, fever, and headache. Those reported in 1% to 5% of patients included nausea, pain, dyspnea, vomiting, back pain, hypotension, abdominal pain, dizziness, angina pectoris, dyspepsia, increased sweating, cardiac arrest, ventricular tachycardia, cardiac failure, injection site pain, rash, confusion, and constipation. Many of these are frequent sequelae of acute ischemic heart disease, and/or concurrent medications and may or may not be attributable to Indium In 111 MYOSCINT administration. Only one patient experienced adverse events (i.e., dry mouth, sweet taste) that were felt to be definitely related to Indium In 111 MYOSCINT.

Adverse events that occurred in ≥0.5% of the 1318 patients that were felt to be definitely, probably, or possibly-related to Indium In 111 MYOSCINT included injection site pain (0.8%) and fever (0.6%). Administration of Indium In 111 MYOSCINT was not discontinued in any patient due to an adverse event.

OVERDOSAGE

The maximum amount of MYOSCINT that can safely be administered has not been determined. The maximal recommended intravenous dose of Indium In 111 in a single dose is 2.2 mCi (81 MBq).

DOSAGE AND ADMINISTRATION

The recommended intravenous dose of Indium In 111 MYOSCINT is 2 mCi (74 MBq) with a range of 1.8 to 2.2 mCi (67 to 81 MBq). The activity of each dose should be measured by a suitable radiation calibration system just prior to administration. Administer Indium In 111 MYOSCINT as an intravenous bolus over less than one minute. Do not administer by slow intravenous infusion or in conjunction with another drug solution.

Radiation Dosimetry

The estimated absorbed radiation doses, at the time of Indium In 111 expiration to an adult patient weighing 70 kilograms, from an intravenous dose of 2 mCi (74 MBq) of Indium In 111 MYOSCINT, including maximal contributions from Indium In 114m/114 as radionuclide impurity, are shown in the following table. The radionuclide impurity limit for Indium In 114m/114 is not greater than 0.16% at the time of expiration. The effective dose equivalent (EDE) for 2 mCi Indium In 111 MYOSCINT is 1.92 rem (19.2 mSv), which includes 0.3 rem (3.0 mSv) from maximal impurity levels (0.16% of Indium In 114m/114).

Table 7
RADIATION DOSIMETRY

Tissue	Rad/2 mCi	mGy/74 MBq
Kidneys	8.8	88
Liver	4.5	45
Spleen	3.4	34
Red marrow	3.2	32
Heart wall[1]	1.5	15
Bladder wall[2]	1.4	14
Lung	1.4	14
Bone	1.0	10
Small intestine	0.9	9
Ovaries	0.8	8
Uterus	0.8	8
Testes	0.4	4
Thyroid	0.4	4
Total Body	0.8	8

[1] Heart wall and heart chamber contents were source terms.
[2] Bladder content was the source term. Assumes 5 urinary voids per day.

Preparation For Use

INDIUM In 111 CHLORIDE MUST BE OF HIGH PURITY TO ASSURE PROPER PRODUCT PERFORMANCE. The use of high purity Indium In 111 Chloride manufactured by Mallinckrodt, Inc. (Catalog No. N132) or Medi-Physics, Inc. (Catalog No. INS.1PA or INS.1PAF) is required. The Indium In 111 Chloride should be used only to radiolabel MYOSCINT (Imciromab Pentetate) and should not be injected directly into the patient. Indium In 111 Chloride should not be used after its expiration date.

Parenteral drugs should be inspected visually for particulate matter and discoloration prior to administration. Because MYOSCINT is a protein solution, it may develop a few fine translucent particles which have been shown not to affect its potency. MYOSCINT should be filtered prior to use through a low protein-binding 0.2 or 0.22 micrometer (µm) filter. (See paragraph 10 below.)

Preparation of Indium In 111 MYOSCINT should be done using waterproof gloves, adequate shielding of radioactivity, and aseptic techniques. Prior to radiolabeling, the two vials should be allowed to reach room temperature.

1. Required Materials, Not Supplied:
   a. Indium In 111 Chloride (Mallinckrodt, Inc. or Medi-Physics, Inc.).
   b. 2 sterile 1 mL syringes
   c. Lead shield for 11.5 mL (8R) vial
   d. Dose calibrator set for Indium In 111
   e. Gelman ITLC-SG strips, 1.5 x 10 cm.
   f. Closed chamber for chromatography
   g. 0.1M Sodium citrate, pH 5.0
   h. pH paper in the 5.0 pH range or pH meter
   i. Low protein-binding 0.2 or 0.22 µm filter
   j. 21-23 gauge sterile needles
   k. Shielded syringe 2-10 mL.
2. Affix the label "Indium-111 MYOSCINT. Caution Radioactive Material" to the vial containing citrate buffer.
3. Remove the plastic caps from both vials using aseptic technique.
4. Remove the MYOSCINT from its vial by withdrawing (1 mL) with a syringe and inject into the vial containing citrate buffer.
5. Mix the contents by gently inverting the vial several times. Place in a lead shield bearing the label supplied.
6. Add 2.5 mCi (92.5 MBq) of Indium In 111 Chloride to the vial. It is essential to use high purity Indium In 111 Chloride at a concentration of about 10 mCi (370 MBq) per mL (at calibration) from the recommended source.
7. Mix the contents by gently inverting the shielded vial several times and allow to stand for at least 10 minutes at room temperature.
8. Measure the radioactivity of the Indium In 111 MYOSCINT in the vial and record on the shield label. Because MYOSCINT contains no antibacterial preservatives, it should be formulated immediately prior to use. The solution must be used within 8 hours of preparation or discarded in accordance with appropriate regulations pertaining to the disposal of radioactive waste. Refrigeration of Indium In 111 MYOSCINT is not necessary.
9. In order to determine the radiochemical purity of Indium In 111 MYOSCINT, instant thin layer chromatography (ITLC) should be performed by the following techniques:
   a) Using a soft lead pencil, gently mark the origin and the finishing line of the Gelman ITLC-SG strips.
   b) Fill a clean chamber with 0.1 M sodium citrate to a depth of approximately 0.5 cm. The pH of the buffer solution should be tested occasionally to assure that a pH level of 5.0 is maintained.
   c) Employing aseptic techniques, draw approximately 0.1 mL Indium In 111 MYOSCINT solution into a shielded syringe to allow for a single drop to be expressed from the tip of a 21 23 gauge needle. The drop of solution should be placed at the origin of the ITLC strip. The drop represents approximately 370-740 Kbq (10-20 µCi) of Indium In 111 Chloride.
   d) Once the drop has been applied, immediately place the spotted ITLC strip in the chamber containing buffer with the origin at the bottom. Cover the chamber and allow the buffer to migrate to the top line on the ITLC strip. (Note: MYOSCINT origin must be above the buffer solution level.)
   e) Remove the ITLC strip from the chamber and cut it in half dividing the front and origin. Count both halves in the dose calibrator.
   f) Calculate the results as follows:

      [Kbq (µCi) origin] ÷ [Kbq (µCi) origin + Kbq (µCi) buffer front] x 100

      = % In-111 that is protein bound.

      At least 90% of the Indium In 111 must be protein bound in order for the product to be administered to a patient.
10. Prior to injection, filter by withdrawing the Indium In 111 MYOSCINT through a low protein-binding 0.2 or 0.22 micrometer (µm), sterile, non-pyrogenic filter into a shielded syringe. Remove the filter, put a new needle on the syringe, and measure the dose before injection. Discard waste materials (i.e., filter, needles, etc.) in accordance with appropriate regulations pertaining to the disposal of radioactive waste.
11. Indium In 111 MYOSCINT may be administered intravenously as formulated. Alternatively, the solution may be further diluted up to a maximum of 5 mL with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, and then administered intravenously.

Image Acquisition and Interpretation

The recommended imaging times are at approximately 18 to 24 hours and at 48 hours after Indium In 111 MYOSCINT administration. In the Phase 3 trial, approximately 50% of images were diagnostic at 18 to 24 hours. In the case of non-diagnostic images at 24 hours, e.g., due to insufficient blood pool clearance, imaging should be conducted at 48 hours.

Imaging should be performed with a gamma scintillation camera with adequate detector head shielding equipped with at least 37 photomultiplier tubes, a medium energy collimator optimized for Indium In 111 photons, and if possible a sodium iodide crystal at least 3/8 inch (9.5 mm) in thickness and a dual pulse height analyzer.

Appropriate parameters for acquisition of planar images are:

- Dual Pulse Height Analyzer set at 173 keV and 247 keV (photo peaks of Indium In 111)
- 20% symmetric windows
- Three views acquired; anterior, 45° left anterior oblique, and left lateral or 70° left anterior oblique
- Time per acquisition; minimum of 10 minutes per view (good statistics are necessary to allow accurate image interpretation)

Note: Single photon emission computed tomography (SPECT) imaging is optional, although the performance characteristics of Indium In 111 MYOSCINT were not evaluated in the Phase 3 trial with this technique. For SPECT imaging, a rotating gamma camera equipped with a medium energy collimator should be employed. Acquisition requires at least 30 minutes. Fifteen to 20 percent symmetric windows should be centered at the 173 and 247 keV photopeaks.

In evaluating Indium In 111 MYOSCINT images using the 3 planar views (anterior, 45° left anterior oblique, and left lateral) patients with acute myocardial infarction display 3 distinct patterns of uptake. These patterns of uptake correspond to infarctions that result from occlusions within the vascular territories of the 3 major coronary arteries. The characteristics seen with anterior myocardial infarction are intense anterior wall uptake in the anterior and lateral views and septal uptake in the 45° left anterior oblique view. Anterior infarctions often also have less intense uptake visible overlying the inferior wall region in the anterior view, which is due to septal uptake seen *en face* in this view. The typical pattern seen with an inferior myocardial infarction is intense inferior wall uptake in all 3 views. With lateral myocardial infarction, uptake is present in all 3 views, but the LAO 45 view localizes the infarction to the lateral wall. In the lateral view, the site of uptake is seen *en face*, often producing a diffuse "smudge-like" uptake pattern.

For SPECT imaging, coronal slices from base to apex and simultaneously acquired sagittal slices from septum to lateral wall can be used to identify regions of myocardial Indium In 111 MYOSCINT uptake.

See also under PRECAUTIONS for information on Persistent Localization, Localization in Unstable Angina and Other Potential Causes for Uptake.

HOW SUPPLIED

MYOSCINT (Imciromab Pentetate) is supplied as a single dose kit containing two vials. (NDC 0045-0310-09). The MYOSCINT vial contains 0.5 mg of Imciromab Pentetate in 1.0 mL of 10 mM sodium phosphate buffer, 145 mM sodium chloride, and 10% (w/v) maltose (pH 6.5) with no preservatives. The citrate buffer vial contains 1.0 mL of 0.2 M sodium citrate buffer solution (pH 5.0).

Storage

Store kits in a refrigerator between 2° and 8°C until use. DO NOT FREEZE. Do not use beyond the expiration date stamped on the box.

CAUTION

Federal law prohibits dispensing without prescription.

REFERENCES

1. Radioactive Decay Data Tables: A Handbook of Decay Data for Application to Radiation Dosimetry and Radiological Assessments. Kocher, D.C. Technical Information Center, U.S. Dept. Of Energy 1981, DOE/TIC-11026.
2. Antimyosin Imaging in Acute Transmural Myocardial Infarctions: Results of a Multicenter Clinical Trial. Johnson LL, Seldin DW, Becker LC, LaFrance ND, Liberman HA, James C, Mattis JA, Dean RT, Brown J, Reiter A, Arneson V, Cannon PJ, Berger HJ. *J Am Coll Cardiol.* 1989;13:27-35.
3. Myocardial Injury: Quantitation by Cell Sorting Initiated with Antimyosin Fluorescent Spheres. Khaw BA, Scott J, Fallon JT, Gahill SL, Haber E, Homcy C. *Science.* 1982;217:1050-1053.

Manufactured by Centocor B.V., Leiden, The Netherlands

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