



LeukoScan[®], sulesomab

Kit for the Preparation of Technetium-99m Labelled LeukoScan

Sterile, Non-pyrogenic,

Lyophilized Powder for Intravenous Use after Reconstitution with Pertechnetate [^{99m}Tc]

Radiodiagnostic Agent, Infectious Disease Imaging Agent

DESCRIPTION

LeukoScan[®] is a radiodiagnostic agent consisting of a murine monoclonal antibody Fab' fragment, sulesomab, formulated to be labelled with technetium-99m. The active component, sulesomab, is a Fab' fragment generated from IMMUN-3, a murine IgG₁ monoclonal antibody produced in murine ascites. IMMUN-3 is purified from the ascitic fluid and is digested with pepsin to produce F(ab')₂ fragments and subsequently reduced to produce the 50,000-dalton sulesomab. Each vial contains the non-radioactive materials necessary to prepare one patient dose. LeukoScan is a sterile, lyophilized formulation, containing 0.31 mg of sulesomab per vial and includes 0.22 mg stannous chloride dihydrate, 3.2 mg potassium sodium tartrate tetrahydrate, 7.4 mg sodium acetate trihydrate, 5.5 mg sodium chloride, glacial acetic acid (trace), hydrochloric acid (trace), 37.8 mg sucrose, nitrogen (vacuum). The imaging agent, technetium-99m LeukoScan [technetium-99m sulesomab] is formed by reconstitution of the contents of the LeukoScan vial with 0.5 mL sodium chloride for injection USP followed by the addition of 1100 MBq of sodium pertechnetate [^{99m}Tc] in 1 mL of Sodium Chloride for Injection, USP. The resulting solution has a pH of 4.5-5.5 and is intended for intravenous use only. Following administration, the labelled antibody can be visualized by common nuclear medicine instrumentation.

Physical Characteristics of Technetium-99m

Technetium-99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging is listed in the following table.

Principal Radiation Emission Data		
Radiation	Mean % Per Disintegration	Energy (keV)
Gamma-2	89.07	140.5

External Radiation

The specific gamma ray constant for technetium-99m is 0.19 mGy/MBq-hr at 1 cm. The first half-value thickness of lead (Pb) for Technetium-99m is 0.017 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in the following table. For example, the use of 0.25 cm of Pb will decrease the external radiation exposure by a factor of about 1000.

Radiation Attenuation by Lead Shielding	
Shield Thickness (Pb) 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 correct for physical decay of this radionuclide, the fractions that remain at selected time intervals after the time of calibration are shown in the following table.

Physical Decay Chart: Technetium-99m Half-Life 6.02 Hours			
Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501	18	0.126

*Calibration Time

PHARMACOLOGY

The antibody (IMMU-MN3) recognizes an antigenic structure shared by a surface glycoprotein (NCA-90) of granulocytes and the tumor marker, carcinoembryonic antigen (CEA). In a single-group, open-label, uncontrolled study of 53 patients with acute or chronic infections of unknown origin or extent, a 0.25 mg dose was shown to be appropriate for clinical use. *In vitro* studies have demonstrated that LeukoScan has no effect on granulocyte function, but LeukoScan does appear to bind more avidly to activated rather than resting granulocytes.

In clinical trials involving over 350 patients assessed for human anti-mouse antibody (HAMA), no significant induction of HAMA to antibody fragments has been observed nor has there been any elevation of HAMA levels to the fragment in patients with pre-existing HAMA. Patients who have previously received murine monoclonal antibody products, are more likely to have HAMA. In subjects with HAMA, there may be a greater chance of hypersensitivity reactions and diminished efficacy in imaging.

PHARMACOKINETICS

Pharmacokinetic studies were performed after the intravenous administration of the product. The distribution half-life was approximately one hour, the elimination half-life was approximately 20 hours; the route of excretion is essentially renal with 41% of the radiolabel excreted in urine over the first 24 hours after administration.

CLINICAL TRIALS

On the basis of two controlled clinical trials of LeukoScan to demonstrate the safety and effectiveness of this product for defining the presence and location of osteomyelitis, in a total of 175 evaluable patients, LeukoScan had a sensitivity of 88.2%, a specificity of 65.6%, an accuracy of 76.6%, a positive predictive value of 70.8%, and a negative predictive value of 85.5%.

In a subgroup of patients in whom LeukoScan was compared directly to the currently available ¹¹¹In-labelled (occasionally ^{99m}Tc-labelled) autologous white blood cell (WBC) scanning test, LeukoScan showed a statistically significant increase in sensitivity over that achieved by WBC scanning (87.7% vs. 72.6%, p = 0.003 by McNemar's Test), with no discernible decrease in specificity as compared to WBC imaging (67.1% vs. 69.4%).

The clinical results indicate that among different presentations of osteomyelitis, LeukoScan can show different results. The product is more sensitive (93.9% vs. 80.6%), but less specific (51.6% vs. 72.9%), in diagnosing osteomyelitis in patients with diabetic foot ulcers than in patients with other sites of long bone osteomyelitis. However, there is an equivalent diagnostic accuracy between these two presentations (77.5% vs. 75.8%, respectively). This difference is perhaps explained by the anatomically and pathophysiology more complicated clinical setting of osteomyelitis in the diabetic foot, making differentiation of soft tissue and bone infection more difficult than in other presentations of long bone osteomyelitis.

An evaluation of potential clinical impact of LeukoScan demonstrated that LeukoScan could change clinical management in 50.2% or improve clinical outcome in 43.4% of 175 evaluable patients with suspected osteomyelitis involving the phalanges (19.4%), metatarsals (32.0%), tarsals (12.6%), tibia/fibula (16.6%), femur (4.0%), axial skeleton (8.6%) and elsewhere (6.8%). In 49.7% of the patients, LeukoScan was presumed to provide clinical benefit not achievable by other available diagnostic imaging methods, with the potential that the diagnosis could have been made by LeukoScan alone in 70.3% of the patients. These benefits were also accompanied by a substantial reduction (85.4%) in the number of patients who would require other diagnostic imaging procedures.

Since LeukoScan cross-reacts with CEA, it should be borne in mind that it may interact with CEA producing tumors.

INDICATIONS AND USAGE

Use in diagnostic imaging for the investigation of suspected osteomyelitis in long bones and in feet in patients including those with diabetic foot ulcers.

CONTRAINDICATIONS

LeukoScan should not be administered to patients who are hypersensitive to products of murine origin or to technetium-99m.

PRECAUTIONS

General

Anaphylactic and other hypersensitivity reactions can occur following administration of mouse protein to patients. Although serious reactions of this type have not been observed in clinical trials after LeukoScan administration, allergic reactions have been reported in post-marketing experience (**see ADVERSE REACTIONS**). Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of this agent.

Limited data are available regarding the safety and efficacy of readministration. Readministration should only be considered in patients whose sera are negative for human anti-mouse antibody (HAMA) elevation in the fragment assay. The overall radiation dose received by the patient over time should also be taken into account. HAMA should be determined before repeated administration of LeukoScan.

The components of LeukoScan are sterile and non-pyrogenic. It is essential to follow preparation directions carefully and to adhere to strict aseptic procedures during preparation of technetium-99m LeukoScan. The contents of the vial are intended only for use in the preparation of technetium-99m LeukoScan and are not to be administered directly to patients.

The contents of the vial before preparation are not radioactive. However, after pertechnetate [^{99m}Tc] is added, adequate shielding of the preparation must be maintained. Appropriate safety measures should be used to minimize radiation exposure to clinical personnel and patients, consistent with proper patient management.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides.

The product has been formulated to function only when the required amount of pertechnetate [^{99m}Tc] is added to the complete content of each vial. Any change in the ratio of the ingredients, adulteration of the vial's content, including extreme temperature changes for storage after opening the vial, or reduction of the administered dose, will likely result in an ineffective product.

Imaging Interpretation

General:

Areas of potential false-positive (FP) readings may be observed near the major bloodpool organs at very early imaging times, near the sites of antibody fragment metabolism (kidneys), and in the intestines and gallbladder.

Imaging Performance by Imaging Time

There was substantial agreement between the planar imaging performance for osteomyelitis at the two time points (1-2 hr and 5-8 hr), suggesting that one can image once between 1-8 hours.

False-Positive Images

False-positive results were more frequent in diabetic patients with suspected osteomyelitis complicating foot ulcers than in other patients with suspected osteomyelitis of long bones.

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 LeukoScan, and they should be advised to discuss prior use of murine-based antibody products with their physicians (see Heterologous Protein Administration). The safety and efficacy for repeated use of LeukoScan has not been established.

Heterologous Protein Administration

The presence of HAMA and human anti-mouse fragment antibodies have not been reported in patients receiving LeukoScan. It is possible that serious allergic reactions could result in anaphylactic shock, serum sickness or death. In addition, patients who have previously received murine monoclonal antibody products are more likely to have HAMA. When considering the use of LeukoScan in patients who have previously received murine antibody-based products a HAMA fragment assay should be performed. Physicians should be aware of the potential for HAMA to increase the risk of allergic reactions and to alter clearance and biodistribution. The quality or sensitivity of the imaging study may then be compromised.

Drug/Laboratory Test Interactions

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

LeukoScan may interfere with serum assays for assessment of serum levels of CEA. Therefore, any determination of serum CEA should be made prior to injection with LeukoScan. Assays for serum CEA should not be performed within 7 days after injection of LeukoScan.

No data are available on possible drug interactions. Do not mix or administer LeukoScan 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate the carcinogenic or mutagenic potential of technetium-99m sulesomab or to determine its effects on fertility in males or females.

Use in Pregnancy

Category B2. LeukoScan is contraindicated in pregnancy. Animal reproductive toxicity studies have not been performed with LeukoScan, and there have been no studies in pregnant women. Any woman who has missed a period should be assumed to be pregnant unless proven otherwise. Alternative techniques that do not involve ionizing radiation should be considered.

Use in Lactation

^{99m}Tc is excreted in human milk during lactation; therefore, LeukoScan should not be used in lactating mothers. Before administering a radioactive medicinal product to a mother who is breast feeding, consideration should be given whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast feeding should be interrupted and the expressed feeds discarded.

Pediatric Use

Safety and effectiveness in children below the age of 18 have not been established. Therefore, the use of LeukoScan is contraindicated in children.

ADVERSE REACTIONS

The following adverse events were reported in the clinical trials and considered at least possibly related to LeukoScan: eosinophilia (3), monocytosis (1), rash (1). None of these were considered serious, and all resolved without sequelae.

Post-marketing experience currently comprises greater than 30,000 vials sold, with two reports of self-limiting allergic reactions.

OVERDOSAGE

The maximum amount of technetium-99m LeukoScan that can be administered safely has not been determined. In clinical trials, single doses of 1.0 mg of LeukoScan radiolabelled with 900 ± 200 MBq of technetium-99m were administered to 11 patients with various types of infection and there were no adverse reactions at this dose.

In the unlikely event of a radiation overdose being administered with technetium-99m LeukoScan, the absorbed dose to the patient may be reduced by increased oral or intravenous intake of fluids to promote excretion of the radiolabel.

DOSAGE AND ADMINISTRATION

LeukoScan is reconstituted with 0.5 mL isotonic sodium chloride injection. Following reconstitution, 1 mL sodium pertechnetate [^{99m}Tc] is added.

The recommended adult dose is 0.25 mg of Fab' fragment labelled with 900 ± 200 MBq of pertechnetate [^{99m}Tc] (approximately 1.2 mL). The radiolabelled solution is administered as an intravenous injection. After injection, any remaining portion of the reconstituted solution should be discarded.

LeukoScan can be injected ten minutes after reconstitution and should be used within 4 hours following reconstitution. Use of the product more than 4 hours after reconstitution may adversely affect imaging quality. The product should be reconstituted only as prescribed using the exact amount of pertechnetate [^{99m}Tc] added to the entire vial. The reconstituted preparation can be kept at

room temperature prior to infusion. The preparation is sterile, non-pyrogenic and contains no bacteriostatic preservative.

Immediately prior to administration, the patient dose should be measured in a dose calibrator. Prior to patient administration, radiochemical purity must be $\geq 90\%$ by Instant Thin Layer Chromatography (ITLC).

Immunoscintigraphy, using planar and SPECT techniques, should be performed one to eight hours after injection.

Parenteral products should be inspected visually for foreign particulate matter and discoloration prior to administration, and not used if these occur.

Directions for Use

Read complete directions thoroughly before starting the preparation procedure. All procedures should be conducted using aseptic technique and standard precautions for handling radionuclides.

Preparation of Technetium-99m LeukoScan

1. Required Materials, Not Supplied
 - a. Technetium-99m, oxidant-free
 - b. 2, 1-mL shielded, sterile syringes
 - c. Alcohol (or germicidal) swabs
 - d. Lead shield for 3-mL vial
 - e. Sodium Chloride for Injection, USP
 - f. 10- μ l pipette
 - g. Silica gel impregnated glass fiber strips, 1 x 9 cm
 - h. Acetone
 - i. Chromatography jar
 - j. Gamma counter
 - k. Dose calibrator
 - l. Counting tubes
 - m. Sterile 1- and 2-mL disposable syringes
2. Clean the rubber closure of each vial with an alcohol wipe. For reconstitution of lyophilized powder, with a sterile disposable syringe add 0.50 mL of saline injection into the shielded LeukoScan 3-mL vial. The vials are sealed under a low pressure nitrogen atmosphere. If a vacuum is not observed when the vial is pierced, the vial should be discarded.
3. Swirl and shake the vial contents for 30 seconds to insure dissolution.
4. Obtain at least 1000 MBq of freshly eluted sodium pertechnetate [^{99m}Tc] eluate from any commercial source which has been eluted within the past 24 hours. Using saline injection, bring the final volume of eluate solution to 1.0 mL.
5. Add the 1.0 mL sodium pertechnetate [^{99m}Tc] eluate into the shielded vial, shake and allow the labelling reaction to proceed for ten minutes. Total volume in vial should now equal 1.5 mL.
6. Based on the activity measured in the activity calibrator, withdraw a sufficient amount of the product to provide the desired activity (see Dosage and Administration). Technetium-99m LeukoScan can be used after ten minutes and should be used within four hours after preparation. Technetium-99m LeukoScan can be stored at room temperature after formulation.
7. After radiolabelling the antibody, dilute a 10 μ l sample with 1.5 mL saline. Determine the radiochemical purity by Instant Thin Layer Chromatography on silica gel impregnated glass fiber strips, 1 x 9 cm using acetone as the solvent. When the solvent front is within 1 cm of the top of the strip, remove it, cut it in half and place each into a glass tube. Count each tube in a gamma scintillation counter, dose calibrator or

radiochromatogram analyzer. Calculate the percent free technetium as follows:

$$\% \text{ Free Technetium} = \frac{\text{Activity in top half of strip} \times 100}{\text{Total Activity}}$$

The radiolabelled product should be discarded if it contains more than 10% free technetium.

8. After use, the container should be disposed of as radioactive waste.

Image Acquisition

There was essentially no difference in the detection of the presence or absence of osteomyelitis between the 1-2 hour timepoint and the 5-8 hour timepoint after injection. This suggests that imaging can be accomplished anytime between one and eight hours after injection (at the convenience of the nuclear medicine department and the patient).

RADIATION DOSIMETRY

The estimated absorbed radiation doses to an average adult patient (70 kg) from an intravenous administration of LeukoScan labelled with 750 MBq of technetium-99m are provided in Table 1. These dose estimates assume a urinary bladder voiding interval of two hours. These values were calculated according to Medical Internal Radiation Dosimetry.

Table 1 Summary of Normal Organ Dosimetry to an Average Adult Patient (70 kg) from an Intravenous Dose of Technetium-99m LeukoScan [Dose Estimate from 13 Subjects 26 Administrations]	
Organ	Average Dose (µGy/MBq)
Kidneys	44.9
Urinary Bladder Wall	21.5
Spleen	15.7
Heart Wall	11.8
Lungs	10.0
Liver	9.0
Bone Surfaces	8.0
Adrenals	7.2
Red Marrow	7.1
Pancreas	6.8
Thyroid	6.7
Gall Bladder Wall	6.2
Uterus	5.9
Ovaries	4.9
Small Intestine	4.8
Stomach	4.8
Upper Large Intestinal Wall	4.7
Lower Large Intestinal Wall	4.7
Thymus	4.5
Total Body	4.2
Muscle	3.5
Testes	3.0
Breasts	2.8
Brain	2.4
Skin	2.1
Effective Dose (µSv/MBq)	8.0

PRESENTATION

Package containing one (1) vial, with a single-use dose of 0.31 mg lyophilized sulesomab. The product should not be used beyond the expiration date printed on the label.

EXPIRY

The expiry date for this kit stored at 2°C-8°C is 48 months from the day of manufacture.

STORAGE

Store at 2°C-8°C. Do not freeze.

To reduce microbiological hazard, use as soon as practicable after reconstitution and radiolabelling. If storage is necessary, hold at 2°C-8°C for not more than four hours.

Contains no antimicrobial agent. Use once and discard any residue. Product is for single use in one patient only.

Disposal of all radioactive wastes should be carried out in accordance with the NHMRC "Code of Practice for the Disposal of Radioactive Wastes by the User (1985)."

MANUFACTURER

This product is manufactured by Immunomedics, Inc., 300 American Road, Morris Plains, New Jersey, USA.

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AUST R 82071

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Supplier

LeukoScan is supplied in Australia by:

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Australian Radioisotopes (ARI) is a trade name used by the Australian Nuclear Science and Technology Organisation (ANSTO), which is located at Lucas Heights, Sydney. ARI manufactures and markets radioisotopes produced in ANSTO's research reactor, HIFAR, and in its National Medical Cyclotron.

