CEA-Scan®
(Arcitumomab) 8/99

For the Preparation of Technetium Tc 99m Arcitumomab.
Sterile, Non-Pyrogenic, Lyophilized Powder for Intravenous Use Only.

DESCRIPTION

CEA-Scan® is a radiodiagnostic agent consisting of a murine monoclonal antibody Fab′ fragment, Arcitumomab, formulated to be labeled with Technetium Tc 99m. The active component, Arcitumomab, is a Fab′ fragment generated from IMMU-4, a murine IgG_1 monoclonal antibody produced in murine ascitic fluid supplied to Immunomedics, Inc., by Charles River Laboratories. IMMU-4 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 Arcitumomab. Each vial contains the non-radioactive materials necessary to prepare one patient dose. CEA-Scan® is a sterile, lyophilized formulation, containing 1.25 mg of Arcitumomab and 0.29 mg stannous chloride per vial, with potassium sodium tartrate tetrahydrate, sodium acetate trihydrate, sodium chloride, acetic acid, glacial, hydrochloric acid, and sucrose. The imaging agent, Technetium Tc 99m CEA-Scan®, Technetium Tc 99m Arcitumomab, is formed by reconstitution of the contents of the CEA-Scan® vial with 30 mCi of Tc 99m sodium pertechnetate in 1 ml of Sodium Chloride for Injection, USP. The resulting solution is pH 5-7 and for intravenous use only. Following administration, the labeled antibody can be visualized by common nuclear medicine instrumentation.

Physical Characteristics of Technetium Tc 99m

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.[2] 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 Tc 99m is 0.78 R/mCi-hr at 1 cm. The first half-value thickness of lead (Pb) for Technetium Tc 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 Attentuation**
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 Tc 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	0.130

*Calibration Time

CLINICAL PHARMACOLOGY

IMMU-4 is reactive with carcinoembryonic antigen (CEA), a tumor-associated antigen the expression of which is increased in a variety of carcinomas, particularly of the gastrointestinal tract, as well as in fetal gastrointestinal tissues and in certain inflammatory states (e.g., Crohn's disease, inflammatory bowel disease, post-radiation therapy to the bowel), and can be shed and detected in the serum.[3,4] Assays of serum levels of circulating CEA are performed to obtain prognostic information following potentially curative surgical resection and as an adjunct to monitoring for recurrent disease in patients who have undergone curative resection of colorectal cancer.[5] Many cross-reactive, but genetically distinct, CEA variants have been described in the literature, including nonspecific cross-reactive antigen (NCA) and meconium antigen (MA).

IMMU-4 is specific for the classical 200,000-dalton CEA that is found predominantly on the cell membrane. The IMMU-4 antibody does not demonstrate cross-reactivity with NCA or with MA.[6] The Technetium Tc 99m CEA-SCAN® product complexes circulating CEA (less than 50% complexation was observed with plasma CEA levels up to 2000 ng/ml, and is not detectable at serum CEA levels below 250 ng/ml) and binds to CEA on the cell surface.

Use of the Fab′ fragment minimizes induction of human anti-mouse antibody (HAMA). Of over 400 patients evaluated, less than 1% of the patients were sensitized, as demonstrated by lack of induction of HAMA reactive with mouse-IgG-fragment[7,8] (See ADVERSE REACTIONS.) The pharmacokinetics of the Fab′ fragment (as compared to intact immunogloblin) minimizes liver metabolism and the Fab′ fragment clears rapidly from the blood.[9] Pharmacokinetic studies were performed after the intravenous administration of the product. At 1, 5 and 24 hours after infusion, the blood levels were 63%, 23%, and 7% of the injected dose (percent injected dose/liter blood), respectively. The initial half-life was approximately one hour; the terminal half-life was 13 ± 4 hours, with 28% of the radiolabel excreted in the urine over the first 24 hours after administration.

CLINICAL STUDIES

CEA-Scan® (Arcitumomab) was evaluated for imaging efficacy and safety in four clinical trials, two of which were Phase 3, one in patients with known disease[8] and the other in patients with occult disease.[8] These imaging studies were conducted to evaluate the presence, location and extent of colorectal cancer, primarily in the liver and extrahepatic abdominal and pelvic regions.[8] Patients eligible for these studies had no prior exposure to murine proteins or murine antibody products. The imaging protocol in both studies was the same. Whole-body planar images were to be obtained at 2-5 hours and 18-24 hours post-injection, with acquisition of 300K counts per view during the initial planar views and 200K counts per view for the late planar images. The protocols required Single-Photon Emission Computed Tomography (SPECT) images of the head, thorax, abdomen and pelvis at 2-5 hours post-injection.

Performance Characteristics in Patients with Evidence of Disease Detected by Standard Modalities:

An open-label, multi-center, single arm trial designed to evaluate the safety and efficacy of Technetium Tc 99m CEA-SCAN® was performed in patients with histologically confirmed colorectal cancer and evidence of primary and/or metastatic disease detected by physical examination, colonoscopy, and/or standard radiologic studies. A total of 222 patients received a 1-mg dose of the antibody labeled with 20-30 mCi of Technetium Tc 99m. The primary analysis of imaging performance and potential clinical utility focused on

the 122 patients in whom surgical/histopathological evaluation was performed. In patients with at least one site of recurrent or metastatic colorectal cancer identified by standard diagnostic modalities [SDM] (in 95% of patients, this was CT), CEA-Scan® showed an imaging sensitivity of 78% (90/115), a specificity of 86% (6/7), an accuracy of 79% (96/122), a positive predictive value of 99% (90/91), and a negative predictive value of 19% (6/31). When used in conjunction with SDM (identification of potentially malignant lesions by SDM and/or CEA-Scan®), the combination showed an imaging sensitivity of 97% (111/115), a specificity of 29% (2/7), an accuracy of 93% (113/122), a positive predictive value of 96% (111/116), and a negative predictive value of 33% (2/6).

While a formal study exclusively for patients with primary presentation of cancer of the colon or rectum has not been performed, 23 such patients were included in this study. The primary tumor was visualized in 18 of 23 patients by CEA-Scan®. In addition, 11 of these patients had metastatic disease identified at surgery. CEA-Scan® correctly identified at least one metastatic lesion in each of the 11 patients, including 10 patients who had liver metastases.

Performance Characteristics in Patients with Negative or Equivocal Evidence of Disease on Standard Diagnostic Studies:

A single-arm, open-label, multi-center clinical trial designed to evaluate the safety and efficacy of CEA-Scan® (Arcitumomab) for detection of malignant lesions was performed in patients with a history of colorectal carcinoma and presumptive evidence of recurrence or metastasis, primarily due to an elevated and/or rising serum CEA level and negative or equivocal findings on standard radiologic evaluation (CT, MRI, ultrasound). The presence or absence of tumor in one or more sites was determined by histological confirmation from "second-look" surgery, biopsy or laparoscopy, in 88 patients.

Of these 88 patients, 63 had histologically-confirmed malignant lesions. Of these 63, 40 patients had malignant lesions identified on the CEA-Scan® (sensitivity 63%). In four of these 40 patients, reevaluation of the most recent CT scans revealed evidence of disease. Of the 25 patients in whom surgical exploration was negative, CEA-Scan® incorrectly identified a site of disease in 11 (specificity 56%). In this population, the predictive value of a positive CEA-Scan® was 78% (40/51) and the predictive value of a negative CEA-Scan® was 38% (14/37). These data are presented in Table 1.

Table 1
88 Surgically Evaluated Patients with Occult Disease*

		CEA-Scan®		
		Negative	**Recurrence**	**TOTAL**
Surgical Findings	**No disease**	14	11	25
	Recurrence	23	40	63
	TOTAL	37	51	88

*By definition SDM were negative or equivocal for entry; however on review, 4 patients had positive findings on CT scan

Imaging Performance by Region Based Upon Combined Results of the Phase 3 Studies:

The data from the Phase 3 studies were combined to provide an integrated assessment of the imaging characteristics of CEA-Scan® in the abdomen, pelvis, and liver (Table 2).

Table 2
Sensitivity and Specificity of CEA-Scan® (per lesion analysis)

		Abdomen	**Liver**	**Pelvis**	**Overall**
CEA-Scan®	**Sensitivity**	**44/96 (46%)**	**132/211 (63%)**	**62/103 (60%)**	**240/419 (57%)**
	Specificity	**95/112 (85%)**	**96/107 (90%)**	**69/93 (74%)**	**262/314 (83%)**

In general, CEA-Scan® was more sensitive and less specific in the abdomen and pelvis than CT[8]; however, direct comparisons of the performance characteristics of SDM to CEA-Scan® are difficult to interpret, since the results of SDM were entry criteria for both Phase 3 protocols.

Complementarity Analyses Based Upon Combined Results of the Phase 3 Trials:
Analysis of the complementary use of CEA-Scan® with SDMs showed that lesions identified in this population by both CT and CEA-Scan® were significantly more likely to be confirmed as cancer at surgery (positive predictive value (PPV) = 146/150, 97%) than the group of all lesions identified by CT scan (PPV = 200/233, 86%) or all lesions identified by CEA-Scan® (PPV = 240/292, 83%). When the scan results were discordant for the presence of a lesion and when both were negative in a region, the frequency with which tumor was found was lower (see Table 3).

Table 3
Lesions* Detected by CT and/or CEA-Scan® in Surgically Explored Patients

Radiologic Findings		Surgical Findings: Sites without tumor at surgery	Surgical Findings: Histologically confirmed tumor†	Total
CT Negative	CEA-Scan® Negative	233	125 (35%)	358
	CEA-Scan® Positive	48	94 (66%)	142
CT Positive	CEA-Scan® Negative	29	54 (65%)	83
	CEA-Scan® Positive	4	146 (97%)	150
Total		314	419	

* Negative lesions derived from number of potential sites of involvement per region explored
† Percentage of patients with histologically confirmed malignant lesions

In the detection of liver metastases, when added to CT scan evaluation, CEA-Scan®(Arcitumomab) indicated the presence of liver metastases in 18 additional patients of whom 10 actually had liver metastases. Thus, addition of CEA-Scan® increased sensitivity from 55/83 (66%) to 65/83 (78%), but decreased specificity from 113/126 (89%) to 105/126 (83%).

Resectability Analysis:
After the studies were completed and analyzed, criteria were developed to assess the potential for curative resection (based on scans and/or surgical findings), and the data were reanalyzed to assess the role of CEA-Scan® in the pre-surgical evaluation of patients for possible curative resection of recurrent or metastatic disease. A patient or diagnostic scan was scored as resectable (R) if there were $\leq$4 lesions in the liver or only 1 region of abdominal or pelvic involvement, non-resectable (NR) if there were >4 liver lesions or 2 or more regions of involvement, and negative (N) if there was no evidence of disease. The patient assessment was based upon surgical exploration or procedures and pathologic findings.[10]

If lesions were considered present when identified by either CT or CEA-Scan®, CEA-Scan® in combination with CT correctly classified a greater percentage of patients with resectable disease (66% vs. 47%) and a greater percentage of patients with non-resectable disease (47% vs. 19%) compared with CT alone. However, adding CEA-Scan® to CT scan increased the frequency of incorrect identification of disease, among those patients with no disease at surgery, from 15% of patients to 32% of patients. Comparative data regarding the predictive values of CT and of CT plus CEA-Scan® for the absence of metastatic disease, the presence of resectability or of non-resectable disease are provided in Table 4. The predictive value of the combination of the two scans for the absence of malignant disease (i.e., both

negative studies) was greater than for CT alone (67% vs. 38%), whereas the predictive value of findings of resectable or non-resectable disease on CT alone were similar to those of the combination.

Table 4
Comparison of Resectability Determinations in 209 Surgically Explored Subjects According to CT and CT plus CEA-Scan®

Surgical Findings	CT scan Findings			Percentage Correct by Surgical findings	CT plus CEA-Scan‡			Percentage Correct by Surgical findings
	Negative	Resectable	Non-resect		Negative	Resectable	Non-resect	
Negative	**40**	7	0	**40/47 (85%)**	**32**	**12**	**3**	**32/47 (68%)**
Resect.	38	**42**	7	**42/89* (47%)**	**8**	**59**	**18**	**59/89* (66%)**
Non-resect.	28	26	**14**	**14/73* (19%)**	**8**	**27**	**34**	**34/73* (47%)**
Percentage Correct by Scan result †	**40/106 (38%)**	**42/77* (55%)**	**14/26* (54%)**		**32/48 (67%)**	**59/102* (58%)**	**34/59* (58%)**	

*Denominators include some subjects with the "correct" resectability assessment based upon incorrect scan findings
†The percentage of scans for which the resectability status was correct, which is analogous to predictive value for resectability status
‡Lesions identified by either SDM and/or CEA-Scan® were considered positive

Based on the data obtained in the resectability analysis (Tables 4 & 6), the management paradigm (Table 5) was developed to evaluate the potential utility of CEA-Scan® as an adjunct to CT in the resectability analysis.. As noted in the paradigm, when CT and CEA-Scan® were discordant, the CEA-Scan®, by itself, was not to be relied upon.

Table 5 Management Paradigm Evaluated

Imaging Result	Course of Action†
CT + CEA-Scan® concordant for resectability	Operate
CT + CEA-Scan® concordant for non-resectability	Do not operate
CT + CEA-Scan® concordant for absence of disease	Wait and repeat evaluation in 2-3 months
CT+ CEA-Scan® discordant for resectability	Biopsy critical lesion(s) or perform additional study
CT + CEA-Scan® discordant for absence of disease	Biopsy unconfirmed lesion(s)

†The management of any individual should be based on all the available information.

Among the 209 patients with surgical exploration and/or biopsy of lesions, 106 (51%) had CT and CEA-Scan® findings which were concordant, i.e., CT and CEA-Scan® identified the lesions in the same location with similar extent of involvement or both failed to identify any evidence of disease. When CEA-Scan® and CT were concordant, 29 of 31 (94%) patients without disease, 29 of 37 (78%) patients with resectable disease, and 17 of 38 (45%) of patients with non-resectable disease were correctly identified. The predictive value of concordant SDM and CEA-Scan® for absence of disease was 64% (29/45; 95% confidence interval = 50-78%), for the presence of resectable disease was 66% (29/44; 95% CI=52-80%), and for the presence of non-resectable disease was 100% (17/17; 95% CI= 80-100%) [see Table 6].

Table 6 Resectability Determination when CT and CEA-Scan® are Concordant† (n=106)			
Surgical Findings	Concordant CT and CEA-Scan® Findings (n=106)		
	Negative	Resectable	Non-resect
Negative (n=31)	29	2	0
Resectable (n=37)	8	29	0
Non-resectable (n=38)	8	13	17
Total	45	44	17

†CT and CEA-Scan® identified the lesions in the same location with similar extent of involvement or both failed to identify any evidence of disease.

Readministration

Forty-four patients received two injections of CEA-Scan® at a median interval for 11.5 months (range 6-27 months). No serious adverse events and no evidence of HAMA to CEA-Scan® (HAMA <74 ng/mL of ImmuSTRIP fragment assay) were reported following the second injection. Paired imaging studies from the first and second administration were available for 35 of the 44 subjects. In 9% (3/35) of patients, the second imaging studies revealed a change in the pattern of CEA-Scan® distribution which differed from that typically seen after the first injection; specifically, there was more rapid clearance of radiotracer from the blood pool and increased localization of radiotracer in the kidneys. There are insufficient data to determine the etiology for the differences observed and this is under current investigation. The ability of CEA-Scan® to detect the presence, location, and extent of tumor in patients with this pattern of altered biodistribution is not known.

INDICATIONS

CEA-Scan® (Arcitumomab) is indicated, in conjunction with standard diagnostic evaluations (e.g., additional imaging evaluation), for detection of the presence, location and extent of recurrent and/or metastatic colorectal carcinoma involving the liver, extrahepatic abdomen and pelvis in patients with a histologically confirmed diagnosis of colorectal carcinoma. CEA-Scan® provides additional information in patients with no evidence of disease by standard diagnostic modalities (SDM) in whom recurrence or metastasis is suspected based upon elevated or rising serum CEA, and in patients with evidence of metastatic or recurrent disease on SDM. A retrospective analysis suggests that these data can be useful in the evaluation of patients in whom surgical intervention (biopsy, exploratory laparotomy and surgical resection) is under consideration.

CEA-Scan® is not indicated for the differential diagnosis of suspected colorectal carcinoma or as a screening tool for colorectal cancer. CEA-Scan® is not intended for readministration or for assessment of response to treatment. (see PRECAUTIONS)

CONTRAINDICATIONS

CEA-Scan® should not be administered to patients who are hypersensitive to products of murine origin or to Technetium Tc 99m.

WARNINGS

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 CEA-Scan® administration, 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.

PRECAUTIONS

General

CEA-Scan® is to be interpreted in conjunction with standard diagnostic modalities. A negative or positive CEA-Scan® by itself should not be utilized in the diagnostic evaluation of colorectal cancer. Discordant results are substantially less predictive than concordant results.

CEA-Scan® should not be used as a screening test for colorectal cancer.

There is limited experience with readministration of CEA-Scan® (see CLINICAL STUDIES).

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

The contents of the vial before preparation are not radioactive. However, after Tc 99m pertechnetate 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.

Imaging Interpretation

General

There are limited data to determine the imaging characteristics and efficacy of the CEA-Scan® (Arcitumomab) in detection of lesions outside of the abdominopelvic cavity.[7,8]

Areas of potential false-positive readings, particularly with planar imaging, may be observed near the major bloodpool organs (heart, major vessels, etc.) at very early imaging times, near the sites of antibody fragment metabolism (kidneys and urinary bladder), and in the intestines and gallbladder. Late imaging may also aid in the evaluation of suspected normal bowel activity.

With regard to imaging of tumor near the kidneys or urinary bladder, it is advisable to have the patient void urine prior to acquisition of imaging data to decrease bladder activity. Careful SPECT imaging near the kidneys and bladder has been helpful.

Porta Hepatis Region

Precise localization of lesions in the region of the porta hepatis has been difficult. Lesions within the porta hepatis region may be present within the liver or the portal nodes. At the time of surgical exploration, such lesions (which if nodal would preclude resection of hepatic metastases) should be explored first.

False-Positive Lesions

There were 52 false-positive lesions observed in 41 patients from a total of 209 surgically explored subjects in the two pivotal trials. Thirty-five of these lesions were in occult disease patients. Of the 52 false-positive lesions, 11 were observed in the liver, 17 in the extra-hepatic abdomen, and 24 in the pelvis. A pathological correlate to the lesions was infrequently documented; these included granulomas in the liver (1 instance), adhesions with or without suture granulomas (4 cases), surgical incision site (1 case). Descriptions of false-positive lesions within the abdomen were suggestive of colonic activity in several cases.

Hot, Rimmed, and Cold Lesions

Only hot or rimmed lesions should be considered as positive for tumor. Lesions that are rimmed or cold usually fill in as hot or rimmed, respectively, with time.[8,9] Often, large lesions, due to poor vascularization or central necrosis, will appear to be cold.

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 (e.g., serum CEA assays), 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 CEA-Scan®, and they

should be advised to discuss prior use of murine-based antibody products with their physicians. (see Heterologous Protein Administration)

Heterologous Protein Administration
The presence of HAMA and human anti-mouse fragment antibodies has been reported in patients before and after receiving CEA-Scan® (<1% of patients develop HAMA to the antibody fragment). While hypersensitivity reactions to CEA-Scan® have not been observed to date, it is possible that such reactions could occur, resulting 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 the CEA-Scan® in patients who have previously received murine antibody-based products, physicians should be aware of the potential for HAMA to increase the risk of allergic reactions and to alter clearance and biodistribution. 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.

CEA-Scan® 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 CEA-Scan®. Assays for serum CEA should not be performed within 7 days after injection of CEA-Scan®.

No data are available on possible drug interactions. Do not mix or administer CEA-Scan® 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 Tc 99m Arcitumomab or to determine its effects on fertility in males or females.

Pregnancy - Category C
Animal reproduction studies have not been conducted with CEA-Scan®. It is also not known whether it can cause fetal harm or affect reproductive capacity when administered to a pregnant woman. CEA-Scan® should be used during pregnancy only if, in the opinion of the physician, the information to be gained justifies the potential risk to the fetus. Examinations using a radiopharmaceutical in a woman of child-bearing capability should be performed during the first 8-10 days following the onset of menses, if possible.

Lactation
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. If the use of the product is deemed to be clinically indicated, breast-feeding should be interrupted, the expressed milk discarded, and formula feedings substituted for breast-feeding.

Pediatric Use
Safety and diagnostic accuracy in persons under 21 years of age have not been established.

ADVERSE REACTIONS
In the patients studied with CEA-Scan®, one patient each developed the following minor self-limiting adverse effects: transient eosinophilia, nausea, bursitis, urticaria, generalized itching, headache, upset stomach and fever. Out of a total of over 500 patients receiving the product to date, there has been a single report of an apparent grand mal epileptic seizure in a severely hypertensive patient that was “possibly related” to CEA-Scan® infusion.

Over 400 patients who have received CEA-Scan® have been evaluated for HAMA by Immunomedics using ELISA methodology. Fewer than 1% of the patients showed an elevation of HAMA levels to fragment after being injected with CEA-Scan®. If the physician suspects HAMA based on an adverse reaction or

altered biodistribution pattern, and deems that a HAMA assay is clinically warranted, he/she should telephone Immunomedics, Inc., at 800 327-7211, between 8:30 a.m. and 5:00 p.m. Eastern Standard Time, for information on procedures to be followed for submission of patient serum for assessment of HAMA directed against mouse monoclonal antibody fragments.

OVERDOSAGE

Intravenous infusion of intact IgG and $F(ab')_2$ of IMMU-4 in doses of up to 25 mg or Arcitumomab at doses up to 10 mg have not shown any serious adverse reaction.

DOSAGE AND ADMINISTRATION

CEA-Scan® is reconstituted with sodium pertechnetate Tc 99m solution prior to use. (See section on Preparation of Technetium-Labeled CEA-Scan® [Arcitumomab].) The recommended adult dose is a single dose of 1 mg of Arcitumomab labeled with 20 to 30 mCi of Technetium Tc 99m. Following dilution of the Technetium Tc 99m CEA-SCAN® with 1 ml of Sodium Chloride Injection, USP, the dose is administered as a 2-ml intravenous injection. Alternately, the contents of the vial may be diluted to a total volume of 30 ml with isotonic Sodium Chloride Injection, USP. Intravenous infusion of Technetium Tc 99m CEA-SCAN® diluted to 30 ml with Sodium Chloride Injection, USP, should be performed over a period of 5 to 20 minutes.

CEA-Scan® can be injected five 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 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 ^{3}90% by Instant Thin Layer Chromatography (ITLC). The solution should be inspected visually; if there is particulate matter or discoloration, the preparation should be discarded and the manufacturer should be notified.

Immunoscintigraphy, using planar and Single-Photon Emission Computed Tomography (SPECT) techniques, should be performed at two to five hours after injection; selected additional views may be obtained up to 24 hours (as indicated by earlier imaging).

Radiation Dosimetry

Radiation dosimetry for individual organs is provided below. The values were calculated according to Medical Internal Radiation Dosimetry (MIRD). Data represent the mean of ten patients, with the exception of kidney (nine patients), ovary (eight patients) and testes (two patients).

Summary of Normal Organ Dosimetry (µGy/MBq)

Technetium Tc 99m CEA-Scan®

Organ	Mean	± SD
Bladder	16.6	3.6
Kidney	100.3	31.7
Spleen	15.9	4.5
Liver	10.4	2.9
Red Marrow	9.9	2.0
Lung	7.7	1.9
Ovary	7.7	1.5
Total Body	4.6	0.8
Testes	4.5	0.6

Effective dose equivalent 13.1 µSv/MBq
Effective dose 9.1 µSv/MBq

Guidelines for Safe Preparation and Handling

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 Tc 99m CEA-SCAN®

1. Required Materials, Not Supplied

a. Technetium Tc 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-µl 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. The container for Arcitumomab does not contain preservatives. It is important that the user adhere to strict aseptic procedures during the preparation, withdrawal and administration of the CEA-Scan® product.
3. Obtain 25 to 30 mCi sodium pertechnetate Tc 99m in Sodium Chloride Injection, USP, at a concentration of 30 mCi/ml. With in-house generators: in a 2-ml vial, dilute 25-30 mCi of sodium pertechnetate Tc 99m to a final concentration of 30 mCi/ml with Sodium Chloride Injection, USP. Draw up 1 ml of sodium pertechnetate into a 1-ml shielded syringe (with a permanently affixed needle).
4. Inject 25-30 mCi of sodium pertechnetate Tc 99m in 1 ml into a shielded vial of Arcitumomab to resuspend the contents.
5. Swirl and shake the vial for approximately 30 seconds making sure all sodium pertechnetate Tc 99m is in contact with the antibody. Allow the labeling reaction to proceed for at least five minutes. Add 1 ml of Sodium Chloride Injection, USP, in order to facilitate easy removal. Remove the entire contents of the vial. Assay the product in a suitable dose calibrator.
6. After radiolabeling the antibody, remove a small aliquot and use approximately 1 µL without further dilution for the analysis of free technetium in the sample by Instant Thin Layer Chromatography (ITLC). To minimize any oxidation, the ITLC should be performed as soon as possible after removal of the sample. 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, to ensure that levels of free technetium meet the specifications of less than 10%. When the solvent front is within 1 cm of the top of the strip, remove it, cut it in half and place each half into a glass tube. Count each tube in a gamma scintillation counter, dose calibrator or radiochromatogram analyzer. Calculate the percent free technetium as follows:

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

7. Based on the activity measured in the activity calibrator, withdraw a sufficient amount of the product to provide the desired activity (20-30 mCi of Technetium Tc 99m. Technetium Tc 99m CEA-SCAN® can be used after five minutes and should be used within four hours after preparation. Technetium Tc 99m CEA-SCAN® can be stored at room temperature after radiolabeling.
8. Prior to administration, the solution should be inspected visually for particulate matter and discoloration. If either appear, the vial should be discarded and the manufacturer notified.

Image Acquisition

Planar imaging of the pelvis and abdomen, at two to five hours post-injection with at least 500K counts per view, should be made. Image acquisition in analogue and/or digital word-mode with a 128 x 128 matrix is recommended.

SPECT of the pelvis and abdomen at two to five hours post-injection should also be acquired. SPECT acquisition parameters recommended are: 60 projections in a 360° step-and-shoot technique, 30 seconds per view in a 64 x 64 matrix. Data processing by filtered back-projection and reconstruction in three planes (transaxial, coronal and sagittal) is recommended. Where it is desired to evaluate possible non-specific activity, later imaging may be advisable.

If late imaging is performed (up to 24 hours post-injection), intestinal and gall bladder activity may interfere with true tumor imaging. Therefore, such late images should be compared to those made at earlier times (two to five hours) and interpreted conservatively. Occasionally, bowel and gallbladder activity also may be visualized on the early images.

Due to excretion of the labeled fragment in the urine, the patient should urinate prior to imaging of the pelvis in order to decrease bladder activity.

HOW SUPPLIED

Package containing one (1) vial, with a single-use dose of 1.25 mg lyophilized Arcitumomab. The product should not be used beyond the expiration date printed on the label.

Storage

Store at 2°-8° C. Do not freeze.

Following reconstitution and radiolabeling, the material can be held at room temperature and must be used within four hours following reconstitution.

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Covered by one or more U.S. Patents: 10C007-3
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