ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

HumaSPECT 10 mg, powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kit for the preparation of 99mTc labelled HumaSPECT. Votumumab, the active substance, is a human monoclonal antibody, MAb 88BV59.
HumaSPECT kit contains the following sterile, pyrogen-free components:

- one vial of lyophilised votumumab (12 mg);
- one vial of lyophilised, stannous reagent (0.275 mg);
- one vial of diethylenetriaminepentaacetic acid (DTPA) solution (0.006 mMol, 3 ml);
- one vial of water for injections (5 ml);
- one sterile preparation vial;
- one filter 0.45 µm.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

After reconstitution with sodium pertechnetate [99mTc] solution, HumaSPECT [99mTc] is indicated in patients with histologically proven carcinoma of the colon or rectum for imaging of recurrence and/or metastases.
HumaSPECT [99mTc] is employed, in the above mentioned patients, as an adjunct to standard non-invasive imaging techniques, such as ultrasonography or CT scan, in the following situations.

- Patients with evidence of recurrence and/or metastatic carcinoma of the colon or rectum, who are undergoing an evaluation for extent of disease, such as prior to surgical resection and/or other therapy.
- Patients with suspected recurrence and/or metastatic carcinoma of the colon or rectum in association with rising levels of carcinoembryonic antigen (CEA).

4.2 Posology and method of administration

Preparation and administration of HumaSPECT [99mTc] should be performed by a qualified person in a designated clinical setting.
HumaSPECT is reconstituted with sodium pertechnetate [99mTc] solution prior to use.
The recommended adult dose of HumaSPECT [99mTc] for a 70 kg patient is a single dose of 10 mg of votumumab labelled with 900 to 1300 MBq of Technetium [99mTc]. However, most of the efficacy data have been obtained with an activity of around 1300 MBq. The dose is administered intravenously over 5 minutes and should not be mixed with any other medication during its administration. The recommended imaging time is 14-20 h. following antibody injection. Radioimmunoscintigraphy can be performed up to 24 h. after injection. There is no preparation for the injection procedure and the patient may go home after the injection. The following morning, the patient will return for the imaging session. The patient will be required to rest still on a table for 1 to 2 hours during the scan. The physician may interrupt the imaging session to have the patient urinate or receive an enema if small amounts of radioactivity in the bladder or bowel are interfering with the images.
Readministration is discussed in section 4.4.10.

4.3 Contraindications

- Patients with known hypersensitivity to any constituent of HumaSPECT [99mTc] or to human proteins.
- Pregnancy.
- Lactation (see point 4.6.3)

4.4 Special warnings and special precautions for use

4.4.1 Use of radiopharmaceutical agents

- Radiopharmaceutical agents should be used only by qualified personnel with appropriate government authorisation for the use, preparation and manipulation of radionuclides.
- This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organisations.
- Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

4.4.2 Reconstitution

Prior to use, the contents of the vials are reconstituted to prepare HumaSPECT [99mTc]. The contents of the kit components (vials) are not to be administered directly to patients.

4.4.3 Recommended imaging protocol

For optimal results, HumaSPECT [99mTc] images should be acquired using a large field-of-view gamma camera equipped with a parallel hole, high resolution collimator or a low energy, all-purpose collimator. The camera should be calibrated using the 140 keV photopeak and a 20% symmetric window.
The recommended imaging time after injection of HumaSPECT [99mTc] is between 14 and 20 hours, but can be performed up to 24 hours.
In order to obtain adequate counting statistics, planar images should be acquired in anterior and posterior views for 10 minutes per view. SPECT imaging of selected regions should be acquired in order to provide additional information regarding the location and presence of disease. SPECT imaging is particularly useful in distinguishing non-specific uptake from regions of tumour involvement.
Imaging studies may show activity in the large bowel because of the presence of radioactivity in stool. Therefore, the administration of a cathartic agent prior to imaging may be required.

4.4.4 Tumour specificity

HumaSPECT is not specific for colorectal carcinomas, since the antigen to which it reacts is expressed by other carcinomas. These include various carcinomas of the digestive system (e.g., stomach and colon tumours) and carcinomas of the lung, breast, ovary, and prostate.

4.4.5 False positives

15 (5%) of the 294 patients with at least one site of recurrent colorectal cancer with histopathological confirmation of disease, were classified as false positive.
Among these 294 patients, 49 patients with negative or equivocal CT scans and rising CEA determinations, 5 (10%) were classified as false positive.
False positives were: reactive (3) or normal (1) lymph nodes, liver (1) and ovary (2) cysts, liver focal nodular hyperplasia (1), liver hemangioma (1), liver necrosis (1), liver adenoma (1), normal gall bladder (1), cholangitis (1), small bowel adhesions (1), presacral fibrous tissue (1).
There is a potential for false positive results near the bladder or kidneys. Voiding of urine before image acquisition should decrease activity in the bladder. SPECT imaging of the abdomen and pelvis is recommended in order to distinguish normal anatomical structures from sites of tumour recurrence.

4.4.6 Hot, rimmed and cold lesions

Only hot or rimmed lesions should be considered as positive for tumour, unless other corroborative evidence supports the interpretation of a cold lesion as a site of cancer. Often, large lesions, due to poor vascularisation, will appear to be cold. Metastases to the liver appear as cold lesions, indicating that cold lesions have a high probability of being malignant. They should be interpreted with results from other diagnostic tests. There were no patients observed in the clinical studies with “rimmed” or “hot” hepatic lesions.

4.4.7 Imaging performance of HumaSPECT [99mTc]

- Extrahepatic abdomen and pelvis:
  For patients with evidence of recurrence and/or metastatic carcinoma of the colon or rectum, HumaSPECT [99mTc] alone is significantly more sensitive than CT (80% vs. 62%). It has a 97% positive predictive value (PPV) and has a negative predictive value (NPV) of 41% for an overall accuracy of 80%.
  For patients with suspected recurrence and/or metastatic carcinoma of the colon or rectum in association with rising levels of carcinoembryonic antigen (CEA), HumaSPECT [99mTc] has a sensitivity of 66% for a specificity of 94%. The positive predictive value (PPV) is 97% and the negative predictive value (NPV) is 55% for an overall accuracy of 75%.
- Bone and brain: conventional diagnostic techniques other than HumaSPECT [99mTc] should be used to identify possible bone and brain dissemination of colorectal cancer.

4.4.8 Hypersensitivity
Allergic reactions, including anaphylaxis, can occur in patients who receive monoclonal antibodies. Although serious reactions of this type have not been reported in clinical trials with HumaSPECT [99mTc] to date, medications for the treatment of such allergic reactions should be readily available during administration of this agent.

4.4.9 Human anti-human antibody (HAHA)
The administration of HumaSPECT [99mTc] could potentially induce human anti-human antibodies (HAHA). However, the presence of HAHA (>100 ng/ml) was not detected to date in serum samples obtained in 353 patients tested at baseline and at 3-6 weeks after either single or repeated injections of HumaSPECT [99mTc].

4.4.10 Readministration
Limited data are available regarding repeat administration of HumaSPECT [99mTc] in patients with recurrent colorectal cancer. Twenty nine (29) patients have received a total of 66 injections of HumaSPECT [99mTc], which were administered at intervals of at least one month between injections. To date, no patient who received a repeat injection has developed a positive HAHA titre nor has any increase in the frequency or severity of adverse events been reported when compared to patients who received a single injection. Planar and SPECT imaging demonstrated no alterations in biodistribution following repeat administration.
Readministration may be performed at intervals of not less than one month. The overall radiation dose received by the patient over time should also be taken into account.

4.4.11 Subjects under 18 years of age
Safety and effectivness has not been established in patients under 18 years old.

4.4.12 Renal or hepatic disease
Formal studies have not been performed in patients with renal or hepatic impairment. However, due to the low dose of protein administered and the short half-life of 99mTc, dosage adjustment is probably not necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Formal drug interaction studies have not been performed, but no medicinal product interactions have been described to date.
Test kits for HIV 1 + 2, EBV, HCV, CEA and CA19.9 have been evaluated and experiences show that administration of HumaSPECT [99mTc] does not falsely elevate values of these in-vitro immunoassays.

4.6 Use during pregnancy and lactation

4.6.1 Women of childbearing potential
When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. When uncertainty exists, it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques, which do not involve ionising radiation, should be considered.

4.6.2 Pregnancy
HumaSPECT [99mTc] is contraindicated in pregnancy. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Administration of 900 to 1300 MBq HumaSPECT [99mTc] will give an estimated absorbed dose of approximately 4.8 to 6.9 mGy to an embryo or foetus at an early stage.

4.6.3 Lactation
Before administering a radioactive medicinal product to a mother who is breast feeding, consideration should be given as to 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. It is usual to advise that breast feeding can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1 mSv. Due to the short six-hour half-life of 99mTc, a dose of less than 1 mSv in mother's milk can be expected 48 hours after the administration of HumaSPECT [99mTc].

4.7 Effects on ability to drive and use machines

No known effect.

4.8 Undesirable effects

The most common adverse reaction thought to be related to HumaSPECT [99mTc], was fever which occurred in approximately 1.6% of the patients.
Transient episodes of hypertension considered as related to HumaSPECT [99mTc] administration were observed in less than 1.5% of the patients.
A slight tendency towards leucocytosis have been observed in up to 18% of the patients during the week following the administration of HumaSPECT [99mTc]. Its relationship with the administration of HumaSPECT [99mTc] is possible, but may be also due to surgery.
Other adverse reactions, each of which occurred in less than 1% of the patients, are listed in order of decreasing frequency: elevation in liver function tests, hypotension, bradycardia, nausea, vomiting, hyperbilirubinaemia and injection site reaction.
The overall incidence of adverse reactions reported for repeated administration of HumaSPECT [99mTc] is similar to that observed after administration of single or initial doses.
For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic result.
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations, the current evidence suggests that the adverse effects will occur with low frequency because of the low radiation doses incurred.
For most diagnostic investigations using a nuclear medicine procedure, the radiation dose delivered (effective dose/EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

Intravenous administration of votumumab in doses of up to 100 mg has not shown any serious adverse reactions.
In the unlikely event of the administration of a radiation overdose with HumaSPECT [99mTc], the absorbed dose to the patient may be reduced by increased oral or intravenous intake of fluids to promote excretion of the radiolabel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceutical for tumour detection, ATC code: V09I A01.
Votumumab, also known as MAb 88BV59, is a human monoclonal antibody of the IgG_3 isotype, kappa light chain. It is directed to a tumour-associated complex of antigens, which is expressed differentially by adenocarcinomas.
The antigen recognised by votumumab is a complex of cytokeratin polypeptides in the molecular weight range of 35 to 43 kDa known as CTAA16.88 or CTA #1. This antigen complex reacts with murine monoclonal antibodies specific for cytokeratin 8, 18 and 19 indicating that the epitopes of these cytokeratins are present in this polypeptide complex.
At the concentrations and activities used for diagnostic procedures, votumumab [99mTc] does not appear to exert any pharmacodynamic effects.
Votumumab is not specific for colorectal carcinoma, since the antigen to which it reacts is expressed by other carcinomas (see Section 4.4.4). In *in vitro* immunohistologic studies, votumumab has been found to be reactive with over 90% of colorectal adenocarcinomas and the majority of breast, prostate, lung and gastric carcinomas. Votumumab is generally not reactive with normal adult tissues, but quantitative differences in reactivity with normal glandular epithelium have been noted.
In clinical studies, HumaSPECT [99mTc] was found to localise in recurrent, metastatic, and occult colorectal carcinoma sites. Additional uptake of radioactivity was observed in the liver, kidneys, sites of abscess and inflammation. Other normal variations among individuals include visualisation of the bowel, blood pool and urinary bladder.

5.2 Pharmacokinetic properties

The pharmacokinetics of technetium Tc 99m-labeled Votumumab are characterised by a biphasic elimination pattern with a distribution half-life ($t_{½α}$, 6 ± 4 hr) and relatively long terminal-phase half-life ($t_{½ß}$, 35 ± 11 hr) and mean residence time (MRT, 44 ± 13 hr). The serum clearance is low (Cl, 1.4 ± 0.5 ml/min), and the volume of distribution is small (V_{ss}, 3.4 ± 0.9 L).

Pharmacokinetics are similar in patients who received single and repeated injections, and in male and female patients.

5.3 Preclinical safety data

Single and repeated dose toxicity studies in animals have not identified any toxic effect on any organs. It should be noted, however, that these studies did not assess carcinogenicity, or potential effects on reproductive activity. Votumumab was not found to be mutagenic nor clastogenic in *in vitro* assays.

5.4 Radiation Dosimetry

For this product, the effective dose resulting from an administered activity of 900 to 1300 MBq is typically 8 to 10.4 mSv for a 70 kg individual.
Technetium [99mTc] disintegrates with the emission of gamma radiation with an energy of 140 keV and a half life of 6 hours to technetium [99Tc] which can be regarded as quasi stable.
Radiation dosimetry for individual organs revealed a generally low level of activity. As might be expected for a [99mTc] labelled antibody, it was highest in the kidney and in the urinary bladder. The values were calculated according to Medical Internal Radiation Dosimetry (MIRD).

Table 1: absorbed dose estimates (μGy/MBq) for total body and individual organs following single and repeated intravenous infusions of HumaSPECT [99mTc].

	Organ Dose (μGy/MBq)								
	1st Infusion (N=9)			2nd Infusion (N=8)			All Infusions (N=17)		
Organ	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Adrenals	8	2	5-11	7	2	5-9	7	2	5-11
Brain	2	1	1-3	3	0	2-3	2	0	1-3
Breasts	4	0	4-4	4	0	3-4	4	0	3-4
Gall bladder wall	8	2	4-12	7	1	5-9	7	2	4-12
Lower large intestine wall	4	1	3-6	5	0	4-5	4	1	3-6
Small intestine	5	1	4-5	5	0	4-5	5	1	4-5
Stomach	5	1	4-6	5	1	4-6	5	1	4-6
Upper large intestine wall	5	1	4-6	5	1	4-5	5	1	4-6
Heart wall	17	3	15-22	18	3	15-23	18	3	15-23
Kidneys	29	23	7-79	22	11	8-39	26	18	7-79
Liver	17	8	6-33	14	4	6-21	15	6	6-33
Lungs	13	2	10-17	13	3	11-18	13	3	10-18
Muscle	4	1	3-4	4	0	3-4	4	0	3-4
Ovaries[a]	5	0	5-6	5	0	5-5	5	0	5-6
Pancreas	7	2	5-10	7	1	5-9	7	2	5-10
Red marrow	7	1	6-9	8	1	6-10	7	1	6-10
Bone surfaces	8	1	6-9	8	1	7-10	8	1	6-10
Skin	2	0	1-3	2	0	2-2	2	0	1-3
Spleen	17	12	4-42	13	8	5-28	15	11	4-42
Testes[b]	3	1	1-3	3	0	3-3	3	0	1-3
Thymus	5	1	4-6	6	1	5-7	5	1	4-7
Thyroid	3	1	1-4	3	0	3-3	3	0	1-4
Urinary bladder wall	20	4	12-23	20	3	15-27	20	3	12-27
Uterus[a]	6	0	5-6	6	0	5-6	6	0	5-6
Total Body	4	1	3-5	4	1	4-5	4	1	3-5
Effective Dose (μSv/MBq)	8	1	6-10	8	1	6-9	8	1	6-10

[a] Mean data based on number of female dosimetry patients who received Injection 1 (N=4), Injection 2 (N=4), or all injections (N=8).
[b] Mean data based on number of male dosimetry patients who received injection 1 (N=5), injection 2 (N=4), or all injections (N=9).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Component A, stannous reagent vial:	stannous chloride dihydrate, D-saccharic acid monopotassium salt, and sodium bicarbonate.
Component B, votumumab vial:	antibody 88BV59, sodium chloride, sodium hydrogen phosphate monohydrate, disodium dihydrogen phosphate heptahydrate, lactose monohydrate.
Component C, DTPA solution vial:	diethylenetriaminepentaacetic acid (DTPA), sodium bicarbonate, sodium chloride.

Water for injections, Ph. Eur.

6.2 Incompatibilities

Not known.

6.3 Shelf-life

18 months. Do not use beyond the expiry date marked on the package.
Once reconstituted, the non-radioactive HumaSPECT kit Components A and B should be used within 4 hours for the preparation of technetium Tc 99m votumumab.
The radiolabelled HumaSPECT [99mTc] dose should be used within 1 hour of radiolabelling in order to deliver a 900 to 1300 MBq dose.

6.4 Special precautions for storage

Store HumaSPECT kit at 2 to 8°C. Do not freeze.
Store HumaSPECT [99mTc] (technetium Tc 99m votumumab) at 15 to 30°C in an appropriately shielded container.

6.5 Nature and content of container

HumaSPECT Kit consists of four vials:

1. Component A: a Type I glass vial of lyophilised stannous reagent (0.275 mg) closed by a rubber stopper and an aluminium flip-off seal.
2. Component B: a Type I glass vial of lyophilised buffered votumumab (12 mg) containing lactose closed by a rubber stopper and an aluminium flip-off seal.
3. Component C: a Type I glass vial containing 3.2 ml of an aqueous solution of 0.006mM diethylenetriaminepentaacetic acid (DTPA), closed by a rubber stopper and an aluminium flip-off seal.
4. A flint glass vial containing 5 ml of water for injections, closed by a rubber stopper and flip-top crimp seal.

The contents of each vial are sterile, pyrogen-free and contain no preservatives.
Each HumaSPECT kit also includes a sterile 0.45 µm filter, an empty, sterile preparation vial, 2 preparation vial/patient dose labels, 2 radiation safety labels and a user package leaflet.

6.6 Instructions for use and handling, and disposal

Read complete directions thoroughly before starting the preparation procedure.
All procedures should be conducted using aseptic technique and standard precautions for handling radionuclides.
The contents of HumaSPECT kit are to be used only to prepare a single unit dose of HumaSPECT [99mTc].
The contents of the individual kit components should not be administered directly to the patient.
Parenteral products should be inspected for particulate matter and discoloration prior to administration, and should not be used if this occurs.
Altering the quantity of any component, including the recommended quantity of technetium Tc 99m, used for radiolabelling, may adversely impact imaging results and, therefore, is not recommended.

6.6.1 Method of Preparation and Quality Control

6.6.1.1 Method of preparation

1. Thirty minutes before radiolabelling, bring the refrigerated HumaSPECT kit to room temperature.
2. Remove the flip-off seals and swab the top of the rubber stopper of each vial with an alcohol wipe.

3. With a sterile disposable syringe and needle, reconstitute the contents of the Component A vial, stannous reagent, with 1.2 ml of the water for injections. Swirl gently to dissolve.
4. Transfer 1 ml of this solution to the Component B vial, containing votumumab. Swirl gently to dissolve. Do not shake or vortex. Place the vial in a suitable radiation shield with a fitted cap.
5. Incubate for 45 minutes at 37°C.
6. With a new sterile syringe and needle, add sterile, pyrogen-free technetium Tc 99m (Ph. Eur.) in less than 2 ml, to the Component B vial and shake gently to mix. 1000 to 1500 MBq must be used in order to obtain the recommended activity of HumaSPECT [99mTc] within 1 hour of preparation.
7. Incubate for 5 minutes at 37°C.
8. Remove the vial and with a new sterile syringe and needle, add 3 ml of Component C, DTPA Solution, to the Component B vial and shake gently to mix.
9. Add sufficient sterile, pyrogen-free, 0.9% saline (not provided) to bring the final volume to 6 ml and shake gently to mix. (Subtracting the volume of technetium Tc 99m added in step 6 from 2 ml will give the volume of saline to be added, in millilitres.)
10. Using a 10 ml shielded sterile syringe and needle, remove the entire contents of the Component B vial. Remove the needle and attach the provided 0.45 µm filter and a new needle. Swab the rubber stopper of the preparation vial with an alcohol wipe. Transfer the contents through the filter to the preparation vial also provided in the kit.
11. Using a 10 ml shielded new sterile syringe and sterile needle, withdraw entire dose of HumaSPECT [99mTc]. Remove the needle and attach a new sterile needle to the syringe.
12. Assay the syringe and its contents in a dose calibrator.
13. On an identification label provided in the kit, record the patient's identification, the date and time of assay, the volume and radioactivity in the syringe and the kit lot number. Affix this label to the syringe shield.
14. Calculate, based on decay factors for technetium Tc 99m, the time period within which HumaSPECT [99mTc] should be administered to the patient.

6.6.1.2 Quality Control, Radiopurity by ITLC method.

Determine the radiochemical purity by instant thin layer chromatography on silica gel impregnated glass fibre strip (1 cm X 8 cm) using ITLC buffer solution* (sodium acetate, pH 5). When the solvent front is within 0.5 cm of the top of the strip, remove the strip. Cut in two portions: 1 X 3 cm (top) and 1 X 5 cm (bottom). Count each portion in a gamma scintillation counter, dose calibrator or radioactivity scanner. Calculate the per cent of technetium Tc 99m bound to the antibody.

The radiolabeled product should not contain more than 10% free technetium.

$$\%Tc99m\ bound\ \ to\ antibody\ = \frac{Counts\ \ in\ the\ bottom\ \ portion}{Total\ \ counts\ \ (top + bottom)} \times 100$$

* Prepare solution A by adding 0.3 ml glacial acetic acid to 50 ml of deionised water. Prepare solution B by adding 0.8 g of anhydrous sodium acetate to 100 ml of deionised water. Mix 30 ml of solution A with 70 ml of solution B to obtain ITLC buffer solution.

6.6.2 Disposal

Discard vials, needles and syringes in accordance with local regulations governing radioactive waste.

7. MARKETING AUTHORISATION HOLDER

Organon Teknika, BV
Boseind 15
5281 RM Boxtel
The Netherlands

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR IMPORT AND BATCH RELEASE AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

A. MANUFACTURING AUTHORISATION HOLDER

Organon Teknika, BV
Boseind 15
5281 RM Boxtel
The Netherlands

Manufacturing Authorisation issued on 7 September 1981 by Ministerie van Volksgezondheid en Miliehygeine.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See paragraph 4.2 of Summary of Product Characteristics).

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

HumaSPECT 10 mg powder and solvent for solution for injection,
votumumab

Kit for the preparation of technetium Tc 99m votumumab (human monoclonal antibody 88BV59) presented as powder for solution for injection.

Kit for the preparation of 99mTc labelled HumaSPECT. Votumumab, the active substance, is a human monoclonal antibody, MAb 88BV59.
HumaSPECT kit contains the following sterile, pyrogen-free components:

- one vial of lyophilised votumumab (12 mg);
- one vial of lyophilised, stannous reagent;
- one vial of diethylenetriaminepentaacetic acid (DTPA) solution
- one vial of Water for injections.
- one sterile preparation vial
- one filter 0.45 µm

Component A, stannous reagent vial:	stannous chloride dihydrate, D-saccharic acid monopotassium salt, and sodium bicarbonate.
Component B, votumumab vial:	antibody 88BV59, sodium chloride, sodium hydrogen phosphate monohydrate, disodium dihydrogen phosphate heptahydrate, lactose monohydrate.
Component C, DTPA solution vial:	diethylenetriaminepentaacetic acid (DTPA), sodium bicarbonate, sodium chloride.
Water for injections, Ph. Eur.	

For Intravenous use only.

Keep out of reach of children.

Exp: mm.yyyy

Store at 2-8°C. Do not freeze.

Discard vials, needles and syringes in accordance with local regulations governing radioactive waste.

Organon Teknika, BV
Boseind 15
5281 RM Boxtel
The Netherlands

EU/XXX/XX

Batch N°:

Medicinal product subject to medical prescription.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

HumaSPECT -Component A

Stannous Reagent, lyophilized

Stannous chloride dihydrate 0.275 mg

Lot #:

Exp.: mm.yyyy

Organon Teknika, BV
Boseind 15
5281 RM Boxtel
The Netherlands

Reconstitute with 1.2 ml water for injections

HumaSPECT-Component B

Votumumab, powder for solution for injection 12 mg

Lot #:

Exp.: mm.yyyy

Organon Teknika, BV
Boseind 15
5281 RM Boxtel
The Netherlands

Reconstitute with 1 ml of reconstituted stannous reagent (Component A).

HumaSPECT-Component C

DTPA Solution 0.006 mM3 ml

Lot #:

Exp.: mm.yyyy

Organon Teknika, BV
Boseind 15
5281 RM Boxtel
The Netherlands

HumaSPECT-Diluent

Water for Injections 5 ml

Lot #:

Exp.: mm.yyyy

Organon Teknika, BV
Boseind 15
5281 RM Boxtel
The Netherlands

Use to reconstitute the stannous reagent (Component A)

LABEL FOR STERILE PREPARATION VIAL

HumaSPECT -TC

Patient ID: _____

Kit Lot #:_____

Tc 99m Activity:_____

Volume:_____

Time: _____

Date: _____

Store at room temperature (15 – 30°C)

CAUTION: RADIOACTIVE MATERIAL

B. PACKAGE LEAFLET

Please read this leaflet carefully, it contains important information for you about HumaSPECT-Tc. If you have any further questions, ask your physician or nurse. Keep this leaflet in a safe place, as you might want to refer to it again.

HumaSPECT 10 mg Powder and solvent for solution for injection.
Votumumab.

Excipients:

Component A, stannous reagent vial:	stannous chloride dihydrate, D-saccharic acid monopotassium salt, and sodium bicarbonate.
Component B, votumumab vial:	antibody 88BV59, sodium chloride, sodium hydrogen phosphate monohydrate, disodium dihydrogen phosphate heptahydrate, lactose monohydrate.
Component C, DTPA solution vial:	diethylenetriaminepentaacetic acid (DTPA), sodium bicarbonate, sodium chloride.
Water for injections, Ph. Eur.	

WHAT YOUR MEDICINE CONTAINS

The active substance of HumaSPECT is votumumab, a human antibody.
An antibody is a protein produced by the human body that can bind to foreign invaders such as infection and tumours. You produce many different kinds of antibodies. Some antibodies are produced from the same family of cells to recognise a specific invader and are called "monoclonal". Votumumab, the active ingredient of HumaSPECT, is a human monoclonal antibody, MAb 88BV59, which binds to the surface of certain kinds of tumour cells.
A pharmacist or other qualified personnel at the hospital bound the monoclonal antibody (HumaSPECT) to a radioactive substance called technetium Tc 99m. When it is combined to the radioactive isotope technetium Tc 99m (HumaSPECT [99mTc]) and injected, it finds certain tumour and attaches to them. This helps your doctor make a diagnosis and evaluate the extent of your illness by using a special imaging camera that reveals areas of radioactivity.

WHAT IS HumaSPECT ?

Votumumab, the active substance is a powder for solution for injection.
HumaSPECT kit contains the following sterile, pyrogen-free components:

- one vial of lyophilised votumumab (12 mg);
- one vial of lyophilised, stannous reagent;
- one vial of diethylenetriaminepentaacetic acid (DTPA) solution;
- one vial of water for injections;
- one sterile preparation vial;
- one filter 0.45 µm.

WHY TAKE HumaSPECT ?

HumaSPECT [99mTc] is a radiopharmaceutical imaging agent. It is used to determine the presence and location of tumours in the body derived from the colon or rectum. Shortly after mixing HumaSPECT with the radioactive technetium isotope, the doctor will inject it into your vein. Fourteen to 20 hours later you will be placed on a special table and pictures will be taken with standard nuclear cameras to see where the tumour(s) is (are) located. Before undergoing the scanning procedure, you should urinate.

WHO IS SELLING HumaSPECT ?
Organon Teknika, BV
Boseind 15
5281 RM Boxtel
The Netherlands

WHO IS MANUFACTURING HumaSPECT ?
Intracel Corp.
1330 Piccard Dr.,
Rockville,
Maryland 20850, USA

WHEN *SHOULD HumaSPECT BE USED* ?
HumaSPECT is a human monoclonal antibody which is linked to a radioactive substance called technetium. It is used in patients with tumours of the colon or rectum that have been diagnosed after examination under microscope. The antibody is able to bind to the surface of certain kinds of tumours, called adenocarcinomas, producing a tumour marker. When the radioactive antibody binds to the tumour, your doctor can determine where it is located by using a special imaging camera that reveals areas of radioactivity. The doctor can also determine how much disease there is and if it has spread to other areas of the body. This will help the doctor to determine whether to operate or what other kind of treatment to use.

WHEN SHOULD HumaSPECT NOT BE USED ?
HumaSPECT should not be used if you have a history of allergic reaction to monoclonal antibodies (immunoglobulin), if you are under 18 years of age as it has not been investigated in this group of patients, or if you are pregnant or breast feeding.
No interactions with other medicinal products have been described to date.

MAY HUMASPECT-TC BE USED DURING PREGNANCY OR BREAST FEEDING ?
There is no information on the use of HumaSPECT during pregnancy. HumaSPECT [99mTc] is contraindicated during pregnancy and should not be used if you are trying to become pregnant. If you are able to bear children, you must be using adequate contraception or have a negative pregnancy test prior to receiving HumaSPECT [99mTc].
There is no information on the use of HumaSPECT [99mTc] in women who are breast feeding. It is not known whether HumaSPECT [99mTc] is excreted in human milk. Therefore it is recommended that HumaSPECT [99mTc] is not administered when you are breast feeding. Breast feeding should never take place during the 48 hours following the injection of HumaSPECT [99mTc] as the dose of radiation that will be contained in your milk may be too high. During this period the expressed milk should be discarded.

MAY YOU DRIVE OR USE MACHINES AFTER RECEIVING HumaSPECT [99mTc]?
There is no data to indicate that HumaSPECT [99mTc] would impair your ability to operate your car or other machinery.

THE AMOUNT OF MEDICINE GIVEN
You will receive a single dose of 10 mg of HumaSPECT. It will contain the radioactive isotope technetium in an amount called 900 to 1300 MBq.

HOW IS HumaSPECT USED.
A doctor experienced with the administration of radioactive substances will prepare HumaSPECT and the radioactive isotope technetium. Ten mg of HumaSPECT will be labelled with 900 to 1300 MBq of technetium. HumaSPECT [99mTc] is injected by a needle placed in your vein. The injection will last about 5 minutes. You will be observed after the injection for any side effects. The radiation dose that you receive is approximately the same as you would get if you received commonly used tests such as a chest X-ray. This small amount of radiation is safe to you or anyone with whom you may come in contact and will be gone from the body in about 24 hours.

There is no preparation for the injection procedure and you may go home after the injection. The following morning, you will return for the imaging session. You will be required to rest still on a table for 1-2 hours during the scan. Your doctor may interrupt the imaging session to have you urinate or receive an enema if small amounts of radioactivity in the bladder or bowel are interfering with the images.

HOW OFTEN YOU WILL BE GIVEN HumaSPECT
HumaSPECT is prepared for a single injection. Your doctor may decide to give it to you again after several weeks for a new examination.

ACTION TO BE TAKEN IN CASE OF OVERDOSE.
Intravenous administration of intact votumumab in therapeutic doses of up to 100 mg has not shown any serious adverse reactions.
In the unlikely event of the administration of a radiation overdose with HumaSPECT [99mTc], the absorbed dose to the patient may be reduced by increased oral or intravenous intake of fluids to promote excretion of the radiolabel.

ARE THERE ANY SIDE EFFECTS THAT I MIGHT EXPERIENCE?
There is a very slight risk of allergic type reactions. The most common symptoms include:

- difficulty breathing
- skin rash
- fever
- a rise or fall in blood pressure
- increase in your heart rate
- back pain.

A doctor or nurse will be with you during the administration of HumaSPECT [99mTc] to detect and treat any of these undesirable effects. Less frequently reported undesirable effects include: nausea, vomiting, and elevated blood tests of liver function.
You may experience one or several of these symptoms, be sure to tell your doctor if you do. If another undesirable effect occurs which is not mentioned in this leaflet, please ask your doctor for advice.
Although the antibody recognises some normal tissues, there is no evidence to suggest that there is a risk of developing antibody-related organ damage. There is a very small risk of your body developing antibodies against HumaSPECT [99mTc], and increasing your risk of an allergic reaction if you receive HumaSPECT [99mTc] again in the future. This has not occurred, in over 470 patients who have received single or repeated HumaSPECT [99mTc].

HOW LONG HumaSPECT CAN BE KEPT, AND HOW IT IS STORED ?
HumaSPECT is stored by the hospital in a refrigerator and given to your doctor when he needs it. The hospital can keep the medicine for 18 months at 2-8°C after it is made. The expiry date is printed on the vial. The product should not be used after this date.
Once reconstituted and radiolabelled, the material can be held at room temperature (15-30°C) and must be used within 1 hour following radiolabelling in order to deliver the recommended dose.

DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED