

SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name: Yttrium-90 Glass Microspheres

Device Trade Name: TheraSphere®

Applicant's Name and Address:

MDS Nordion, Inc.
447 March Road
Kanata, Ontario Canada
K2K 1X8

Humanitarian Device Exemption (HDE) Number: H980006

Date of Humanitarian Use Device Designation: Dec. 1, 1997

Date of Panel Recommendation: Not applicable (Refer to Section XI for discussion).

Date of Good Manufacturing Practices Inspection: September 10, 1999

Date of Notice of Approval to Applicant: DEC 10 1999

II. INDICATIONS FOR USE

TheraSphere® is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters.

III. DEVICE DESCRIPTION

TheraSphere® is a therapeutic device consisting of insoluble glass microspheres in which the radionuclide yttrium-90 (Y-90) is an integral constituent. The microspheres have a mean (\pm SD) diameter of 25 μ m (\pm 10 μ m, with less than 5% below 15 μ m and less than 10% above 35 μ m). Each milligram contains between 22,000 and 73,000 microspheres. The TheraSphere® dose is supplied in 0.05 mL of sterile, pyrogen-free water contained in a 0.3-mL vee-bottom vial secured within a 12 mm clear lucite vial shield. TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi), and 20 GBq (540 mCi). Each dose of TheraSphere® is supplied with an administration set. The administration set is a single use delivery system designed to deliver TheraSphere® to the disease site and to minimize radiation exposure to administering personnel. The pre-assembled administration set has inlet and outlet lines that facilitate infusion of the microspheres from the dose vial.

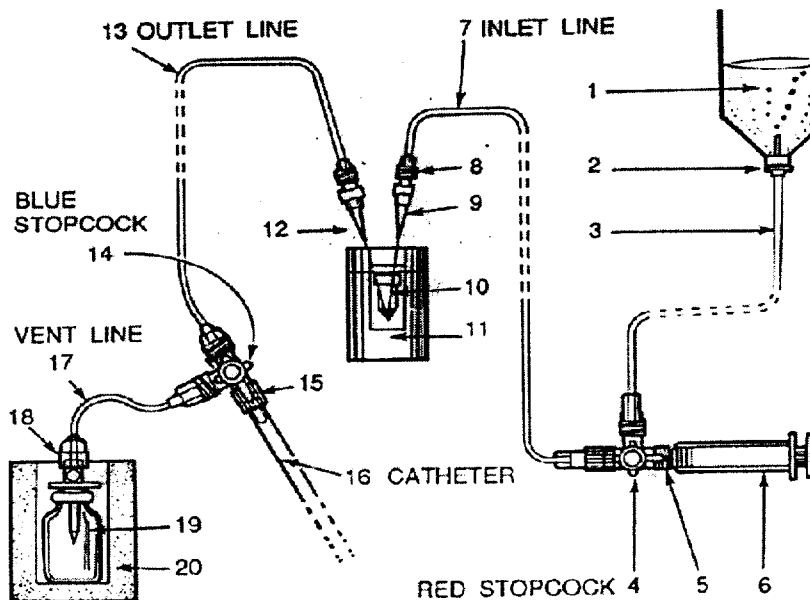
Radiation Dosimetry

Yttrium-90, a pure beta emitter, decays to stable zirconium-90 with a physical half-life of 64.2 hours (2.68 days). The average energy of the beta emissions from Y-90 is 0.9367 MeV. The average range of the radiation in tissue is 2.5 mm, with a maximum range less than 1 cm. One GBq (27 mCi) of Y-90 per kg of tissue gives an initial radiation dose of 13 Gy (1,297 rad) per day. The mean life of Y-90 is 3.85 days. Thus, the radiation dose delivered by Y-90 over complete radioactive decay starting at an activity level of 1 GBq (27 mCi) per kg is 50 Gy (5,000 rad).

Administration Set

The TheraSphere® administration set is a single use delivery system consisting of an inlet set and an outlet set. The inlet set and the outlet set are made up of pre-assembled sterile, apyrogenic components hermetically sealed in a bag and ethylene oxide sterilized. Each dose is supplied with all the components required for administration exclusive of items utilized in the catheterization procedure. Figure 1 is a diagrammatic representation of the contents of the administration set.

Figure 1. TheraSphere® Administration Set



The numbers refer to the following items: 1 - fluid source, 2 - piercing pin, 3 - fluid line, 4 - red three-way stopcock, 5 - free port on the red three-way stopcock, 6 - 5 mL syringe, 7 - inlet line, 8 - check valve, 9 - 20 gauge needle at the free end of the inlet line, 10 - TheraSphere® dose vial, 11 - acrylic vial shield, 12 - 20 gauge needle at the free end of the outlet line, 13 - outlet line, 14 - blue three-way stopcock, 15 - freeport

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on the blue three-way stopcock, 16 - catheter, 17 - vent line, 18 - filter vent assembly, 19 - sterile empty vial and 20 - lead pot.

Principles of Operation of the Device

TheraSphere® is delivered into the liver tumor through a catheter placed into the hepatic artery. This artery provides the main blood supply to the tumor in the liver, as opposed to normal liver parenchyma, which is dependent on the portal vein. TheraSphere®, being unable to traverse the tumor vasculature, is embolized within the tumor and exerts a local beta radiation radiotherapeutic effect with relatively limited concurrent injury to surrounding normal tissue.

Properties of the Device Relevant to the Treatment of the Disease

TheraSphere® is used to treat liver tumors where the blood supply is delivered by the hepatic artery. The size of the microspheres causes them to be embolized in the tumor vasculature and hence, retained within the tumor. The microspheres are not biodegradable and do not redistribute to other organs of the body. The administration set facilitates the transfer of the radioactive microspheres from their container into the tumor via a catheter inserted in the hepatic artery.

Yttrium-90 is an integral component of the glass matrix. Yttrium-90 is a radioisotope well suited for localized radiation therapy. The beta particle emitted during radioactive decay has an average tissue penetration of 2.5 mm and a maximum tissue penetration less than 1 cm. Therefore, this radioisotope is suitable to deliver highly localized radiation doses to tumors while minimizing the damage to surrounding healthy liver tissue.

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

The use of TheraSphere® is contraindicated in patients:

- whose Tc-99 macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract which cannot be corrected by angiographic techniques.
- who show shunting of blood to the lungs which could result in delivery of greater than 16.5 mCi of radiation to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment.
- in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities, bleeding diathesis, or portal vein thrombosis.
- who have severe liver dysfunction or pulmonary insufficiency.

Precautions /Warnings

- Radioactive products should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.
- Adequate shielding and precautions for handling radioactive material must be maintained.
- The TheraSphere® dose vial is supplied secured within a clear acrylic vial shield to limit radiation exposure to personnel. The dose rate at the vial shield surface is still high enough to require caution including the use of tongs and a lead shielded container when possible. The vial should always be stored in a shielded location away from personnel.
- Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately following good radiation safety practices and the area monitored for contamination at the end of the procedure.
- As in the use of any radioactive material, care should be taken to insure minimum radiation exposure to the patient extraneous to the therapeutic objective and to insure minimum radiation exposure to workers and others in contact with the patient.
- Since adequate studies have not been performed in animals to determine whether this device affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this product should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.
- Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Based on clinical and preclinical animal experience with TheraSphere® and other yttrium-90 microspheres, certain adverse reactions have been identified [1-7]. Adverse events that occurred in the 100 Gy HCC (N=22) [8], the Pilot HCC (N=9) [3], and the Mixed Neoplasia (N=4) [9,10] studies are summarized by severity in Table 1.

Table 1
Incidence^a of Treatment-Emergent Adverse Events From Three Studies^b (N=35),
SWOG Toxicity Grading System

Adverse Event	Mild	Moderate	Severe	Life Threatening	Lethal/Fatal	Total
Increased Transaminase (SGOT/SGPT) ^c	14 (40.0%)	14 (40.0%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	33 (94.3%)
Increased Alkaline Phosphatase	18 (51.4%)	9 (25.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	30 (85.7%)
Increased Lactic Dehydrogenase	19 (54.3%)	2 (5.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	24 (68.6%)
Increased Bilirubin	0 (0.0%)	9 (25.7%)	6 (17.1%)	4 (11.4%)	1 (2.9%)	20 (57.1%)
Abdominal Pain	6 (17.1%)	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	16 (45.7%)
Decreased Hemoglobin	8 (22.9%)	4 (11.4%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	15 (42.9%)
Nausea	9 (25.7%)	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	13 (37.1%)
Anorexia	11 (31.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Malaise/Fatigue/Lethargy	5 (14.3%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Other Pain ^d	5 (14.3%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Decreased White Blood Cell	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (28.6%)
Fever, Absence Infection	4 (11.4%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (25.7%)
Increased Creatinine	6 (17.1%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Increased Prothrombin Time	5 (14.3%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Edema	3 (8.6%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	7 (20.0%)
Weight Gain	5 (14.3%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (20.0%)
Gastric Ulcer	1 (2.9%)	0 (0.0%)	4 (11.4%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Other Liver ^d	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Vomiting	4 (11.4%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (17.1%)
Anxiety/Depression	4 (11.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Hemorrhage (Clinical)	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Other Gastrointestinal ^d	3 (8.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Decreased Platelet	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Cough	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Dyspnea	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Insomnia	4 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Weight Loss	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Constipation	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Diarrhea	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Hyponatremia	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Pneumonia	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)	3 (8.6%)
Sweats	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Dysrhythmia	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)
Headache	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
Infection	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)

Abbreviations: SWOG, Southwest Oncology Group; HCC, hepatocellular carcinoma; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

^a For each patient, the highest severity of an adverse event was counted once. Adverse events that were reported by at least two patients in the total population are summarized.

^b Studies: 100 Gy HCC (N=22), Pilot HCC (N=9), and Mixed Neoplasia (N=4).

^c If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a 51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.

^d Other pain included pain in back/lower back (3), epigastric (2), chest (1), legs (1), shoulder (1), stomach (1), toe (1), and musculoskeletal (1). Other liver included hepatitis (2) and ascites (4). Other gastrointestinal included abdominal discomfort (1), early satiety (1), heartburn (1), duodenal ulcer (1), and burping (1).

The introduction of microspheres into the vasculature of the stomach, duodenum or other organs of the gastrointestinal tract can cause chronic pain, ulceration and bleeding. Microsphere shunting to the lungs can cause edema and fibrosis that may not be reversible. Extrahepatic shunting may be identified through the injection of Tc-99 MAA into the hepatic artery [11, 12]. Flow of radioactivity to the

gastrointestinal tract may be avoided by the use of balloon catheterization or other angiographic techniques to block such flow [13]. The use of this product leads to irradiation of both tumorous and normal liver parenchyma. As a result, patients with diseases which compromise the functioning of the non-tumorous liver parenchyma or with very small lesions scattered throughout the normal parenchyma may be at greater risk of liver function impairment.

VI. ALTERNATE PRACTICES AND PROCEDURES

Surgery

The standard curative therapy for hepatocellular cancer is complete resection of the tumor in a patient who has not developed metastatic disease. However, only 15% of patients in high incidence countries and 30% of cases in western countries are candidates for attempts at curative resection. Liver transplantation is an option for the cure of patients with liver-confined hepatocellular cancer who cannot have curative partial hepatectomy. Because of limited access to transplant centers and limited availability of donor organs, liver transplantation benefits only a small minority of patients with hepatocellular carcinoma.

Non-surgical Treatments

Other therapies for hepatocellular cancer includes: 1) systemic chemotherapy, 2) hepatic artery embolization with materials such as lipiodol, angiostat, and gel foam, and 3) chemoembolization where chemotherapeutic agents are mixed with embolizing material.

Chemotherapy

Both single agent therapy with drugs such as FUDR and combination therapy with combinations of drugs including mitomycin, 5-FU, FUDR, doxorubicin, and cisplatin have been used in the treatment of hepatocellular cancer. Single agent therapy with FUDR, [14, 15] a drug which is particularly attractive for intrahepatic therapy because of a 95% first pass hepatic extraction, is capable of inducing responses in as many as 50% of patients; median survivals range from six to seven months. With combination chemotherapy, [16, 17] high orders of response in the range of 60-70% have been reported in small studies. Median survivals for these studies, however, are only approximately eight months. Long-term survival is very rare and intrahepatic chemotherapy is not considered useful except as a palliative measure in hepatocellular cancer.

Embolization and Chemoembolization

Because of the vascular nature of hepatocellular cancer, controlling the tumor by hepatic arterial embolization has been of considerable interest. Embolization of materials such as lipiodol, angiostat, and gel foam have been used to devascularize hepatocellular cancer. [18 - 20]. These approaches result in decreases in serum

alpha fetoprotein (AFP) in as many as 50-90% of cases and patients selected for this treatment have one year survivals ranging from 30-50%. When chemotherapeutic agents are mixed with the embolizing material, anti-tumor responses of 40-90% have been noted [21, 22] and some patients have survival well beyond one year, although median survival rates are less than 12 months. Because of the ability of embolization and chemoembolization to produce substantial anti-tumor responses and some improvement in survival, they have been used as initial therapy in patients who are candidates for hepatic transplantation. This strategy is aimed at controlling the hepatocellular cancer in the liver while the patient awaits an available liver for orthotopic transplantation. Survival data are difficult to interpret in embolization/chemoembolization therapy since some patients are subsequently transplanted. Since transplant is known to have curative potential, it is not possible to assess whether the pretransplant therapy had significant impact on long term survival. In considering survival results reported for embolization, chemoembolization, or any other hepatic directed therapy, it is important to note that there are significant and important patient selection factors which may result in these patients having better survival potential than the general population of patients with hepatocellular cancer. For example, patients with severe underlying liver disease are not candidates for these therapies. Patients for hepatic directed therapies must have good performance status, no extrahepatic tumor and relatively good hepatic function without severe portal hypertension. These patients also must possess the intellectual ability and personal support systems to comply with a complex medical intervention.

Embolization and chemoembolization may be associated with significant toxicity. These therapies cause fever and pain in the post-therapy period in all patients. "Clinical" hepatitis, i.e., elevation in transaminases and/or bilirubin is common. Infections may occur and these therapies are not applicable to patients with portal vein obstruction and must be used with caution in patients with portal hypertension.

VI. MARKETING HISTORY

MDS Nordion has had TheraSphere® available for sale in Canada since 1991. Syncor International, MDS Nordion's distributor for Asia and Mexico, has had TheraSphere® available for sale in Hong Kong since 1995. TheraSphere® has recently been approved for use in Mexico and will be made available for sale by Syncor International.

TheraSphere® has not been withdrawn from marketing for any reason relating to safety or probable benefit of the device.

VIII. SUMMARY OF PRECLINICAL STUDIES

In Vitro Studies

In vitro laboratory testing of TheraSphere® demonstrated excellent chemical and physical stability under simulated use conditions. The results at pH 7 indicated that

the solubility of yttrium from the glass matrix becomes extremely small as the dissolution medium approaches physiologic pH. The release of Y-90 from the activated glass microspheres comprising TheraSphere® production batches was evaluated also. The mean ratio of Y-90 in solution at pH 6 to that in the glass microspheres was 0.00093. This result was in good agreement with the pH 6 removal data obtained with the nonradioactive spheres. This test was performed at pH 6 because at pH 7 and above the solution activity became too small to quantify.

In Vivo Studies

1) An evaluation was performed to examine the translocation of Y-90 from TheraSphere® in Sprague-Dawley rats. The Y-90 was injected via the caudal vein so that the microspheres lodged in the vasculature of the lungs. An average of 90% (SD=11) of the activity delivered (the difference between the activity in the syringe before and after delivery) could be accounted for. Considering the differences between the geometry and composition of the various samples and containers involved, this is a very satisfactory result. In only one case, Rat 11, was activity detected outside the lungs. In this case the activity was around the delivery site. Except for this one case, activity was confined to the lungs. The extent of translocation in the test animals was below the limits of detection using this protocol. No detectable activity was found in the liver of any animal at any time. These results lead to the conclusion that the extent of translocation was 0.1% or less of the total amount delivered. This is a level, which should produce no adverse health effects.

2) Another preclinical study (liver distribution study) evaluated TheraSphere® in normal and tumor-bearing New Zealand white rabbits. The glass microspheres were introduced directly into the hepatic artery of New Zealand white rabbits by means of a catheter placed in the gastroduodenal artery, and were evaluated specifically for their ability to distribute throughout the liver in relative proportion to hepatic blood flow without inducing any acute changes in systemic hemodynamic stability and without inducing changes in local hepatic perfusion due to excessive occlusion of capillary beds.

The results from this study demonstrated that: 1) administering either 140,000 or 460,000 glass microspheres to the rabbit's liver (average weight between 70 and 100 grams) by direct hepatic arterial delivery does not acutely alter systemic blood pressure or heart rate, nor does it occlude the hepatic capillary bed significantly so as to induce alterations in regional hepatic perfusion; 2) although the glass microspheres do not necessarily distribute throughout the liver in direct proportion to regional blood flow patterns as determined by administration of tracer resin microspheres, they do adequately distribute to all lobes of the liver including caudal aspects and peripheral edges; and 3) the glass microspheres tend to be delivered in higher concentrations to central regions of the liver, and to regions with relatively higher local blood flow. This might be of some advantage, as tumors tend to have relatively higher local blood flows.

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3) A small study examined the tolerance of TheraSphere® administration via the hepatic artery in dogs.

The radioactive glass microspheres, in the quantities with the specific activities administered (See Table 3), were well tolerated in all dogs. Signs referable to toxicity were not observed although some abnormalities were observed in serum biochemical parameters. An increase in SGPT was measured in dog 234I. SGPT is an enzyme located in the cytosol of hepatocytes. An elevation is indicative of hepatocellular injury with leakage of the enzyme. Serum alkaline phosphatase consists of several isoenzymes; induction of hepatic alkaline phosphatase is the likely cause of the SGPT elevation in dog 234I. The increased hepatic alkaline phosphatase production observed was probably induced by increased intracanicular hydrostatic pressure. The mechanism in this case is hepatocellular swelling which can occlude bile canaliculi. Taken together these elevated enzymes suggest hepatocellular damage and swelling.

Table 3. Radioactivity Administered to Foxhounds

Dog	Weight (kg)	Mass of Spheres	Activity in Vial	Activity Delivered	Activity in Liver
234C	40	116 mg	52.0 mCi	96	50.0 mCi
234I	25	75 mg	33.6 mCi	95	32.0 mCi
34K	29	79 mg	35.2 mCi	95	33.0 mCi

The extent of hepatocellular damage may be estimated from the SGPT elevation in that the degree of elevation parallels the number of hepatocytes affected. The SGPT elevation does suggest some degree of damage. The elevated SAP (serum alkaline phosphatase) indicates hepatocellular swelling, but the degree of pressure on bile ducts was not severe enough to result in hyperbilirubinemia.

The amylase elevation observed in dog 234C suggests distribution of some microspheres to the pancreas. Amylase is a leakage enzyme that rises in serum in cases of pancreatic cell damage. The pancreatic duodenal artery, a branch of the gastroduodenal, which branches from the common hepatic artery, supplies the pancreas. A mechanism therefore exists for distribution of some glass microspheres to the pancreas. The elevation was small and with the absence of clinical signs indicates minimal damage to the pancreas.

The observation that all hematologic parameters monitored remained within normal limits implies asepsis of the product and delivery procedure. The duration of this preliminary study was insufficient to evaluate any effect on bone marrow stem cells.

4) The appearance of radioactivity in the blood of dogs following administration of Tc-99 MAA microspheres and TheraSphere® via the hepatic artery was also assessed. The data in Table 4 provide some insight into the release of Y-90 from TheraSphere® in vivo. Dogs B & H did not receive any radionuclides; thus their

blood samples represent an estimate of background in this system. The samples from C, I, and K measured through 1/27/86 were all higher than those for B and H. By 2/10/85 all samples had roughly comparable values to those from B and H. This seems to indicate that some Y-90 activity was indeed present following the delivery of TheraSphere®. If the long-lived isotope Tc-99 MAA had been responsible for the initial activity above background, the 14-day decay period would not have resulted in the change observed (neglecting all other elimination mechanisms for Tc-99 MAA). Assuming the worst case, i.e., all elevated activity was due to Y-90, and assuming that the activities observed on 2/10/85 were essentially background, then the blood activity elevation relative to background can be calculated. The column "Elevation" gives the ratio of the initial activity to background indicating that on average the TheraSphere® elevated the blood activity by only 90 percent of background. This indicates a very low level of mobile Y-90 from TheraSphere® delivery into the hepatic artery. This result is in qualitative agreement with the in vitro release studies, which indicate a very low Y release rate at physiological pH. Quantitative comparison would require detailed knowledge of Y absorption and elimination kinetics -- information that is not available.

Table 4. Activity in Blood

Activity observed in serum and plasma samples obtained from dogs in acute toxicity tests.

Date	Dog	Sample	Initial	Activity Decayed	Differ.	Elevat.
1/23	B	Ser	2.5	2.2	0.3	1.1
1/23	H	Ser	2.5	2.2	0.3	1.1
1/23	C	Ser	4.0	2.5	1.6	1.6
1/23	I	Ser	3.9	2.4	1.5	1.6
1/23	C	Pla	3.6	2.1	1.5	1.8
1/23	I	Pla	3.5	1.9	1.5	1.8
1/23	K	Pla	3.2	1.9	1.3	1.6
1/24	C	Pla	4.6	2.5	2.1	1.8
1/24	I	Pla	6.5	2.5	4.0	2.6
1/24	K	Pla	5.3	2.4	2.9	2.2
1/25	C	Pla	4.6	2.3	2.3	2.0
1/25	I	Pla	5.2	2.3	2.9	2.2
1/25	K	Pla	4.3	2.3	2.0	1.9
1/26	C	Pla	4.5	2.3	2.2	2.0
1/26	I	Pla	4.7	2.3	2.4	2.1
1/26	K	Pla	4.5	2.3	2.2	2.0
1/27	C	Pla	3.4	2.3	1.1	1.5
1/27	I	Pla	3.6	2.0	1.6	1.8
1/27	K	Pla	2.8	2.4	0.5	1.2

Initial, Decayed and Difference are activities given in curies times 1011, i.e., 10⁻⁵ microcuries, per ml sample. Date indicates when sample was drawn.

Elevation gives the ratio of the initial activity to the background (Decayed Activity).

There is some indication that the activity levels were highest at 48 through 72 hours after delivery. A linear release rate model predicts a maximum activity outside the liver at 96 hours.

Detailed interpretation of the results of this study must be kept in perspective. The fact is, the activity observed in the blood of dogs C, I, and K were in all cases less than 3 times background. This leads to a large uncertainty in the measurements, making only gross trends observable. The amount of Y-90 in circulation in the dogs studied was extremely small -- very near current limits of detection.

5) A subsequent study evaluated the reaction of canines to the administration of non-radioactive glass microspheres through surgically implanted hepatic arterial catheters. Two dogs were administered at 1.5 times the currently proposed human dose of 5 million spheres and two at 6 times this dose. On a liver weight basis, the dog doses were 3 times and 12 times more than any patient will receive. All dogs were sacrificed one-month post treatment. Liver function tests showed minor changes only, and, at autopsy, there was no evidence of cirrhosis or portal fibrosis in any of the dogs.

6) Additionally, four dogs had hepatic arterial catheters placed angiographically (procedure to be used for most human patients) and were administered glass microspheres at a level 2.5 times (5 times on a liver weight basis) the currently proposed-human dose. The tissue damage observed at necropsy following sacrifice at 48 hours post administration varied from no evident damage to extensive infarction of the gall bladder with focal hepatic infarcts.

7) Pulmonary toxicity was assessed also in dogs. Six dogs were divided into two groups of three each: a high dose group receiving doses of 120, 130 and 168 Gy and a low dose group receiving doses of 31, 33, and 33 Gy. TheraSphere® was delivered into the cephalic vein. In the high dose group, the 168 Gy dog was near death from pulmonary failure on day 96 and was euthanized. The other two dogs in this group were euthanized at day 108. The 120 and 130 Gy dogs showed x-ray changes consistent with pulmonary fibrosis as well as minor blood gas abnormalities. Dogs receiving 31 and 33 Gy showed no changes on chest x-ray or in blood gases or clinical status. Routine pathological examination of the lungs of dogs receiving 31 and 33 Gy were normal (identical to untreated dogs). The high dose dogs had extensive fibrosis. The maximum dose (10 millicuries, ca. 18 - 20 Gy) allowable for patients is below that generating significant symptomatic permanent injury in dogs.

8) Biodistribution was examined in five New Zealand white rabbits which were infused via the hepatic artery with 10 milligrams (1 millicurie) of TheraSphere®. The study organs can be divided into two groups, those with an arterial supply arising at or below the celiac axis and those with an arterial supply outside this region. The first group of organs can contain radioactive glass microspheres and in some cases was observed to contain radioactivity. The other group of organs should

not contain any glass microspheres and, in fact, no activity was observed in any sample. The first group of organs in this study consisted of the spleen, duodenum, pancreas, stomach, colon, ileum, gall bladder, and bile duct while the second group consisted of the lungs and bone marrow. This biodistribution study supports the contention that the rate of release of Y-90 from TheraSphere® is extremely low.

9) Biocompatibility was not tested directly for TheraSphere® but is inferred from extensive studies done with glass fiber, a close analogue to the glass microspheres. These studies found very low pulmonary toxicity. A two-year inhalation study [23] in which animals were allowed to live out their lives found only minimal macrophage reaction without pulmonary fibrosis even at fiberglass dust concentrations in excess of 100 mg/m³. Also no neoplastic reactions were observed. A study of workers with a mean exposure of 20 years showed no significant difference in pulmonary disease over a carefully matched control group [24]. To test for the biocompatibility and tissue reactions of TheraSphere®, four dogs had nonradioactive TheraSphere® delivered through surgically implanted hepatic arterial catheters to evaluate subacute tissue reactions. Each set of two dogs had 3 and 12 times the proposed human dose of 5 million glass microspheres delivered into their livers. All dogs were sacrificed one-month post treatment. Liver function tests showed minor changes only and, at autopsy, there was no evidence of cirrhosis or portal fibrosis in any of the dogs.

Summary of Findings from the Preclinical Studies

A number of preclinical studies were completed on different animal species: rats, dogs, and rabbits. In the rat studies TheraSphere® was delivered into the caudal vein and trapped in the capillaries of the lungs. The activity of the liver, cranial section, caudal section and tail (delivery site) were below the detection limit of the measuring equipment used. An average of 90% of the activity delivered could be accounted for in the lungs since no activity was found in other body parts, the fact that the activity balance did not account for 100% of the activity indicates a systematic error in the bremsstrahlung measurements involved. The dog study determined the radioactivity in the blood of dogs following delivery of TheraSphere® via the hepatic artery. On average, the blood activity was found to be two times background. This indicates a very low level of mobile Y-90 from TheraSphere® into the hepatic artery. The rabbit study involved measurement of the distribution of TheraSphere® in organs. TheraSphere® was delivered into the hepatic artery of white rabbits. The study organs were divided into two groups. Those organs that had an arterial supply at or below the celiac axis, which could convey microspheres, were observed to contain some radioactivity. The second group of organs has their arterial supply outside of the celiac axis. No activity was observed in any sample from these organs. The release of Y-90 from TheraSphere® appears to be negligible. In summary, the preclinical studies have shown that the irradiated yttrium (Y-90) is not displaced from the glass matrix under clinically relevant conditions.

IX. SUMMARY OF CLINICAL STUDIES

A. Overview of TheraSphere® Clinical Studies

Three clinical studies have been conducted with TheraSphere®. All three studies were observational with mortality, response to treatment, and safety as major endpoints. Six study centers participated in these studies with five from Canada and one from the United States (US). All studies were performed in patients with unresectable liver cancer (HCC and metastatic).

The first protocol to begin enrollment was "Phase I Study of Hepatic Arterial Yttrium-90 Glass Microsphere (TheraSphere®) Therapy for Liver Neoplasia", and will be referred to as the "mixed neoplasia study". The mixed neoplasia study recruited patients with carcinoid and colorectal metastatic disease to the liver, as well as primary hepatobiliary carcinoma. The second protocol entitled "A Pilot Trial of Yttrium-90 Microspheres in the Treatment of Primary Hepatocellular Carcinoma" will be referred to as the "pilot HCC study". This study targeted HCC patients. Both protocols required beginning at an initial nominal liver dose of 50 Gy. Based on accumulating multicenter safety data, the dose was escalated in increments of 25 Gy not exceeding a target dose of 100 Gy. These two protocols resulted in 111 patients being treated with TheraSphere®, and comprised the data upon which TheraSphere® gained Canadian approval in 1991. Treated patients from these two protocols are intended to provide supporting safety data.

The third protocol entitled "Phase II Trial of Yttrium-90 Microspheres in the Treatment of Primary Hepatocellular Carcinoma" was approved by the Toronto Hospital Committee for Research on Human Subjects in January 1992, and the first patient was treated on April 3, 1992. Based on the encouraging safety results of the pilot HCC study, the nominal liver dose was set at 100 Gy. This study will be referred to as the "100 Gy HCC study". The last patient under this protocol was treated on April 10, 1996. This study provides the primary clinical safety and probable benefit data.

The main differences between the three protocols, besides dose escalation, are that prior chemotherapy and/or radiation therapy were not allowed in the 100 Gy HCC study. Compared to the pilot HCC study, the mixed neoplasia study required that all patients be evaluated pretreatment with a radionuclide liver scan and be angiographically assessed for lesion vascularity. The 100 Gy HCC and Mixed Neoplasia studies required a pretreatment Tc-99 MAA scan to predict the activity to be delivered to the lungs from the treatment dose. All three protocols were single treatment protocols.

The treatment indication sought for TheraSphere® is for HCC. Diagnosis of HCC was based on cytology, pathology, or the confirmation of a dominant liver mass with an associated serum AFP greater than 1000 ng/dL. The distribution of hepatocellular carcinoma cases from each protocol is as follows: four cases from the mixed neoplasia

study, nine cases from the pilot HCC study, and 22 cases from the 100 Gy HCC study.

B. Mixed Neoplasia [9, 10] and the Pilot HCC [3] Studies

Mixed Neoplasia Study: Objectives and Patient Selection/Exclusion Criteria

The objectives of the mixed neoplasia study were to evaluate the toxicity of Y-90 microsphere therapy and to define, using escalating radiation doses, the maximum tolerated dose of Y-90 glass microspheres administered by hepatic arterial infusion that would be suitable for Phase II-III studies in a similar patient population.

Eligibility criteria for the mixed neoplasia study included:

- histological proof of surgically unresectable metastatic colonic carcinoma of the liver, carcinoid tumor metastatic to the liver, or primary hepatobiliary carcinoma
- hepatic arterial angiography or Tc-99 MAA hepatic arterial perfusion to demonstrate that the hepatic tumor was vascular
- Karnofsky performance status equal to or greater than 60
- peripheral leukocyte count greater than 4,000/mm³
- granulocyte count greater than 2,000/mm³
- platelet count greater than 150,000/mm³
- serum albumin greater than 2.5 g/dL
- bilirubin less than 2 mg/dL
- SGOT less than 6 x normal
- prothrombin time within 3 seconds of control (or correctable with Vitamin K to same)
- serum creatinine less than 2.0 mg/dL.

Patients also had to have a hepatic arterial perfusion scan using Tc-99 MAA or albumin microspheres showing complete perfusion of both lobes of the liver, an F (fraction of Tc-99 MAA activity observed in the lungs relative to the total Tc-99 MAA activity observed) times A (the Y-90 activity to be injected) product of 10 mCi or less, and no detectable Tc-99 MAA activity in the stomach and/or duodenum by gastric air contrast scan. Patients must have terminated any previous chemotherapy or non-hepatic radiation therapy at least four weeks before entering the study and they must have recovered from all toxicity from the previous therapy. Patients who had received previous hepatic radiotherapy were excluded from the study.

Pilot HCC Study: Objectives and Patient Selection/Exclusion Criteria

The objectives of the pilot HCC study were to define the activity of Y-90 microspheres administered by hepatic arterial infusion to patients with hepatocellular carcinoma and to evaluate the toxicity of Y-90 microsphere therapy.

Patients eligible for the pilot HCC study had to have histologic or cytologic proof of primary hepatocellular carcinoma and the disease must have been measurable. The

inclusion and exclusion criteria for this study were comparable to those enumerated above for the mixed neoplasia study.

Population Description and Treatment Administration

From July 1986 to December 31, 1989, a total of 111 patients were treated in these two studies with TheraSphere® in North America. One hundred (100) patients were evaluable (Table 5). The evaluable patients were divided into three categories of tumor type: adenocarcinoma, hepatocellular carcinoma and all other tumor types. The patients were further divided into two dose ranges: less than 80 Gy (35 to 79 Gy) and equal to or greater than 80 Gy (80 to 150 Gy).

Table 5. Evaluable Patients

	<8,000 rads	≥8,000 rads	Totals
Adenocarcinoma	22	50	72
Hepatocellular	7	6	13
Other Tumor Types	5	10	15
Total	34	66	100

Summary of Safety Data

Two patients died during the follow-up period. The deaths were attributed to elevated bilirubin (elevated before TheraSphere® treatment that increased in severity 2 days after treatment and continued until the patient's death 2 weeks later; judged as possibly related to TheraSphere®), and pneumonitis, (death approximately 6 weeks after TheraSphere® treatment; judged as possibly related to TheraSphere®).

In the group of 34 patients treated at < 80Gy 13 patients (38%) had gastric complications, 2 patients (6%) had fevers lasting between 1 and 6 days, and 3 patients (9%) had complications classified as "other." Of those patients with gastric complications 9 had grade 1-2 symptoms and 4 patients developed ulcers. Two of the ulcer patients were managed with medication and 2 required surgical intervention. Of those patient complications listed as other one was ascites. A second patient experienced lethargy and confusion that extended over a nine-day period.

In the group of 66 patients treated at 80 Gy or more 15 (23%) experienced gastric symptoms. This apparently lower incidence of gastric complications may be due to the adoption of a different catheterization technique. A balloon catheter was employed whenever possible in these latter patients to prevent any of the microspheres from entering the right gastric artery. Five of the 15 patients with gastric complications developed ulcers. Three were medically managed and two required surgical intervention. One of the 66 patients experienced a fever possibly due to tumor necrosis as a result of the Y-90 therapy.

Five (8%) of the 66 patients developed complications classified as "other". Two patients developed a "red line" rash on the skin in the area where the catheter used to deliver the spheres was left in place. Normally the catheters are removed

immediately and disposed of with the other radioactive waste. Residual radioactivity remaining in the catheters even after flushing probably resulted in the erythema. One patient had an elevated WBC ascribed to tumor necrosis and one patient had RUQ pain thought due to rapid and significant tumor shrinkage. A fifth patient developed a measles-like rash that was probably due to an antihistamine reaction.

Summary of Probable Benefit Data

Table 6. Therasphere® Median Survival (months)

	Dose < 80 Gy	Dose ≥ 80 Gy
Adenocarcinoma	9.1 (n=22)	9.7 (n=50)
Hepatocellular	3.6 (n=8)	11.1 (n=7)

The fifty adenocarcinoma patients treated at doses of 80 Gy or more had a median survival of 9.7 months and those treated at < 80 Gy had a median survival of 9.1 months (see Table 6). Hepatocellular patients treated at < 80 Gy had a median survival of 3.6 months but those treated at ≥ 80 Gy had a median survival of 11.1 months. Survival of the adenocarcinoma patients is comparable to published survival data for the systemic and intrahepatic infusion of chemotherapeutic agents for the treatment of metastatic liver cancer.

Conclusions for Mixed Neoplasia and Pilot HCC Studies

The data derived from these two studies support the following conclusions with respect to the use of TheraSphere® in the treatment of liver neoplasia:

- TheraSphere® appears to be more efficacious at a dose range of 80 to 150 Gy than at lower doses.
- TheraSphere®, when administered at the 80 to 150 Gy dose range according to the directions does not cause unacceptable toxicities or complications.

C. 100 Gy HCC Study [8]

The objectives of the study were to define the activity of Y-90 microspheres given by the hepatic artery infusion to a previously untreated patient with primary hepatocellular carcinoma, to evaluate the survival of patients treated with Y-90 microspheres, and to evaluate the toxicity of Y-90 microsphere therapy.

Patient Selection and Exclusion Criteria

Eligible patients had to have

- histologically confirmed unresectable hepatocellular carcinoma confined to the liver and at least one measurable lesion
- ECOG performance status 0-3,
- estimated life expectancy greater than 12 weeks,

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- absolute granulocyte count $2.0 \times 10^9/L$ or greater,
- platelet count $100 \times 10^9/L$ or greater,
- prothrombin time (PT) and activated partial thromboplastin time (aPTT) within normal limits,
- bilirubin less than 1.5 x upper normal limit,
- aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP) less than 5 x upper normal limit
- normal pulmonary function defined as no more than 30% greater or less than the expected normal.

Exclusion criteria included

- previous chemotherapy or radiation,
- any contraindication to hepatic artery catheterization such as vascular abnormalities, bleeding diathesis, allergy to contrast dye, or portal vein thrombosis,
- any medical or psychosocial condition, which would not permit the patient to be managed according to the protocol.

Population Description and Treatment Administration

Twenty-two patients were treated in the 100 Gy HCC study. Two patients were excluded from the efficacy analysis due to an unconfirmed diagnosis of HCC. Patient 11017 did not have cytology or pathology results and had an AFP of 35 ng/dL. Patient 11019 had a pathology diagnosis of cholangiocarcinoma. Twenty patients received one TheraSphere® treatment; two patients received a second TheraSphere® treatment based on the principle investigator's discretion.

Three patients had undergone a prior right lobectomy and were being treated with TheraSphere® for a recurrence. The time from recurrence to TheraSphere® treatment was taken as the measure of treatment delay. Nine patients were classified as Okuda stage I and eleven patients as Okuda stage II. The median activity administered was 3.9 GBq and ranged from 2.0 GBq to 9.2 GBq, with two infusions injected into the left hepatic artery, three into the right hepatic artery, and fifteen infusions specified as hepatic artery only. The median liver dose was 104 Gy and ranged from 46 Gy to 145 Gy. All bremsstrahlung scan results were reported as comparable to the pretreatment Tc-99 MAA scans. One patient had known breast cancer at the time of treatment and another patient had prostate cancer. Three patients received either chemotherapy or immunotherapy for progression of their liver cancer after TheraSphere® treatment.

Summary of Safety Data

Three patients (11006, 11019 and 11026) died during the follow-up period. Patient 11026 died approximately two months after TheraSphere® treatment due to radiation pneumonitis (received estimated lung dose of 56.5 Gy); the investigator

judged the death to be definitely related to TheraSphere® treatment. Patient 11019 died approximately two months after TheraSphere® treatment due to a gastric ulcer; the investigator judged the death to be probably related to TheraSphere® treatment. Patient 11006 died approximately five months after TheraSphere® treatment due to hepatitis; the investigator judged the death to be possibly related to TheraSphere® treatment.

TheraSphere® treatment procedures were completed without complications; however, one patient (11013) suffered from a possible angiography contrast agent allergic grade 3 reaction. Seven patients exceeded the protocol stated lung shunt exclusion criteria of 10 mCi during the first treatment with TheraSphere® with activity levels of 11.2, 11.3, 11.8, 14.0, 14.3, 16.4, and 30.5 mCi. These patients received estimated lung doses of 20.8, 21.0, 21.8, 25.9, 26.4, 30.3, and 56.5 Gy, respectively. The accumulated lung doses for the two patients who underwent a second TheraSphere® treatment were 43 Gy (Pt. 11002) and 36 Gy (Pt. 11021).

There were twenty-four grade 3 toxicities in 11 patients, four grade 4 toxicities in four patients, and three grade 5 toxicities, for a total of 31 toxicities of grade 3 or higher in 14 patients. 45.2% of these toxicities were liver related and 19.4% were gastrointestinal. Liver toxicities were primarily elevated enzymes during the week after treatment, while the gastrointestinal toxicities included three ulcers, one ileus, and one nausea. Patient 11021 experienced grade 3 fatigue after the second TheraSphere® treatment.

Summary of Probable Benefit Data

As of February 14, 1997, only two patients remained alive resulting in a median survival of 378 days (95% CI, 209 - 719), with a minimum survival of 49 days and a maximum survival of 1265 days. Based on a stratified Cox survival analysis model; activity ratio, Okuda stage, and liver dose appeared to influence survival by approximately the same magnitude of effect. This effect was measured by the estimated risk ratio for activity ratio (.26), liver dose (.28) and the reciprocal of the estimated risk ratio for Okuda stage (.29).

A sensitivity analysis of the effect of liver dose on survival, taking into consideration the delay of treatment, was performed. The influence of treatment delay did not appear to confound the liver dose trend.

Two patients received a second TheraSphere® treatment. Patient 11002 received a total dose equal to the targeted dose of 100 Gy. However, patient 11021 received two approximately equal doses resulting in a total of 209 Gy.

X. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

Preclinical studies demonstrated that TheraSphere® is designed to prevent leakage of Y-90 from the glass microspheres, and that TheraSphere® is biocompatible and does not cause significant adverse tissue reaction.

The results from preclinical and clinical studies provide evidence of the safety of TheraSphere® in the treatment of patients with surgically unresectable hepatocellular carcinoma. In addition, the probable benefit from the use of TheraSphere® in this patient population outweighs the risks when compared to the safety and probable benefits of currently available alternative therapies.

XI. PANEL RECOMMENDATION:

This HDE was not taken to an Advisory Panel because other radioisotopes, for different etiologies in different patient populations, have been in use in the United States for many years. In addition, the use of embolization is a well-established therapeutic approach for treating other conditions such as vascular bleeding.

XII. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, TheraSphere® will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of injury or illness, and issued an approval order on DEC 10 1999.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See Package Insert (Attachment 1).

XIV. REFERENCES

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