



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: December 30, 1999
From: Humanitarian Device Exemptions (HDE) Staff, ODE, CDRH
(HFZ-403) 1595 '00 JAN -4 P157
Subject: HDE Approval Package (H980006)
To: Dockets Management Branch (HFA-305)

Attention:

Lyle Jaffe
Gloria Ortega
Jennie Butler

The following HDE application was recently approved:

HDE Number: H980006
Docket Number: 99M-5539
Device Name: TheraSphere®
Applicant: DataMedix Corp., U.S. Representative for
MDS Nordion, Inc.

Attached is the following information for this HDE:

Approval Order
Summary of Safety and Probable Benefit
Labeling

If you have any questions, please call me at (301)594-1190
ext. 107.

Marsha Melvin

Marsha Melvin

Attachments

99M-5539

AAV1

APPROVAL ORDER



Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 10 1999

James Goin, Ph.D.
U.S. Representative for MDS Nordion, Inc.
c/o DataMedix Corporation
600 North Jackson Street, Suite 306
Media, Pennsylvania 19063

Re: H980006
TheraSphere®
Filed: August 11, 1998
Amended: September 14 and December 31, 1998; March 19 and April 8, 1999

Dear Dr. Goin:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for TheraSphere®. This device 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. CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device after you have submitted an amendment to this HDE with copies of the approved labeling in final printed form.

The sale, distribution and use of this device are limited to prescription use in accordance with 21 CFR 801.109.

FDA wishes to remind you that failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/ode/hdeinfo.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

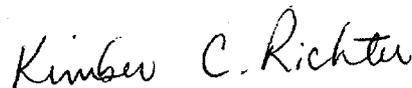
Page - 2 - Mr. Goin

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact John C. Monahan at (301) 594-1212.

Sincerely yours,



Kimber C. Richter, M.D.
Deputy Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

CONDITIONS OF APPROVAL FOR AN HDE

I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment to the HDE. The supplement should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

- 1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or
- 2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but

not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

V. POSTAPPROVAL REPORTING REQUIREMENTS Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

A. ANNUAL REPORT

Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the HDE Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):

1. An update of the information required under §814.102(a) in a separately bound volume;
2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);
3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;
4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and
5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. ADVERSE REACTION AND DEVICE DEFECT REPORTING

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

- (1) A mixup of the device or its labeling with another article.
- (2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and
 - (a) has not been addressed by the device's labeling or
 - (b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

- (3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be included in the "Annual Report" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION

The Medical Device Reporting regulation (MDR) (21 CFR 803) became effective on April 11, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices:

- (1) may have caused or contributed to a death or serious injury; or
- (2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Events subject to reporting under the MDR regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements. FDA has determined, however, that such duplicative reporting is unnecessary. Therefore, whenever an event involving a device is subject to reporting under both the MDR regulation and the "Adverse Reaction and Device Defect Reporting" requirements, the report should be submitted in compliance with Part 803 and identified with the HDE reference number to Food and Drug Administration, Center for Devices and Radiological Health, Medical Device Reporting, PO Box 3002, Rockville, Maryland 20847-3002. For questions regarding the MDR regulation, please call (301) 594-2735.

Events included in periodic reports to the HDE that have also been reported under the MDR regulation must be so identified in the periodic report to the HDE to prevent duplicative entry into FDA information systems.

Copies of the MDR regulation and FDA publications, entitled "An Overview of the Medical

Device Reporting Regulation" and "Medical Device Reporting for Manufacturers," are available on the CDRH WWW Home Page (<http://www.fda.gov/cdrh>), through CDRH's Fact-on-Demand (FOD) at 800-899-0381 (FOD # 336, 1336, 509 and 987) or by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Lane
Rockville, Maryland 20850

SUMMARY OF SAFETY AND
PROBABLE BENEFIT

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.

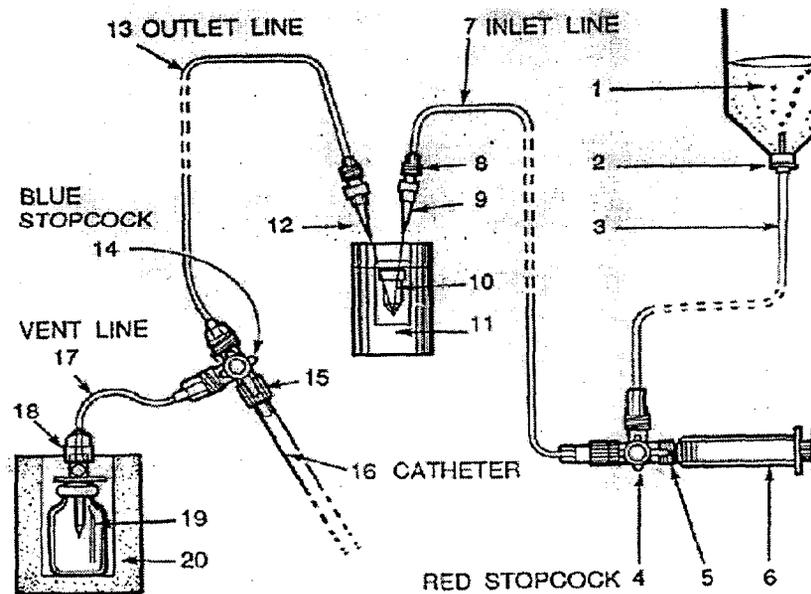
Radiation Dosimetry

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

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/Fat al	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.

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.

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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 $2.0 \times 10^8/L$ 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

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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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LABELING

Package Insert

TheraSphere® Yttrium-90 Glass Microspheres

Humanitarian Device.

Authorized by Federal Law for use in the 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. The effectiveness of this device for this use has not been demonstrated.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training and experience.

DESCRIPTION

TheraSphere® consists of insoluble glass microspheres where yttrium-90 is an integral constituent of the glass [1]. The mean sphere diameter ranges from 20 to 30 μm . Each milligram contains between 22,000 and 73,000 microspheres. TheraSphere® 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 acrylic vial shield. A pre-assembled single use administration set is provided with each dose. TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi) and 20 GBq (540 mCi).

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 yttrium-90 is 0.9367 MeV.

Following embolization of the yttrium-90 glass microspheres in tumorous liver tissue, the beta radiation emitted provides a therapeutic effect [2-6]. The spheres are delivered into the liver tumor through a catheter placed into the hepatic artery that supplies blood to the tumor. The spheres, being unable to pass through the vasculature of the liver due to arteriolar capillary blockade, are trapped in the tumor and exert a local radiotherapeutic effect with some concurrent damage to surrounding normal liver tissue [7-14].

INDICATION

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

CONTRAINDICATIONS

The use of TheraSphere® is contraindicated in patients:

- whose Tc-99 MAA hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract which cannot be corrected by angiographic techniques (see Item 1 under **INDIVIDUALIZATION OF TREATMENT**);
- who show shunting of blood to the lungs which could result in delivery of greater than 16.5 mCi of yttrium-90 to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment (see Item 2 under **INDIVIDUALIZATION OF TREATMENT**);
- in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities, bleeding diathesis, or portal vein thrombosis; and

- 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.
- 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.
- Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately and the area monitored for contamination at the end of the procedure.
- 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.

ADVERSE REACTIONS

Based on clinical and preclinical animal experience with TheraSphere® and other yttrium-90 microspheres, certain adverse reactions have been identified [4-6, 15, 16, 17, 18]. Adverse events that occurred in the 100 Gy HCC (N=22), the Pilot HCC (N=9) [4], and the Mixed Neoplasia (N=4) [3, 11] studies are summarized by severity in Table 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 [19, 20]. Flow of radioactivity to the gastrointestinal tract may be avoided by the use of balloon catheterization or other angiographic techniques to block such flow [21]. 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.

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

Adverse Event	Life					Total
	Mild	Moderate	Severe	Threatening	Lethal/Fatal	
Increased Transaminase (SGOT/SGPT) ^c	14 (40.0%)	15 (42.9%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	34 (97.1%)
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%)	8 (22.9%)	6 (17.1%)	4 (11.4%)	1 (2.9%)	19 (54.3%)
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%)
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%)
Malaise/Fatigue/Lethargy	5 (14.3%)	5 (14.3%)	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	0 (0.0%)	4 (11.4%)	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).

CLINICAL STUDIES

1. 100 Gy HCC Study

- **Objectives:** To define the activity of yttrium-90 microspheres given by hepatic artery infusion to a previously untreated patient with primary hepatocellular carcinoma (HCC); to evaluate the survival of patients treated with yttrium-90 microspheres; and to evaluate the toxicity of yttrium-90 microsphere therapy.
- **Study Design:** Patients with HCC were treated with a target dose of TheraSphere® of 100 Gy by injection through the hepatic artery. Patients underwent laboratory tests, history and physical examinations, and liver ultrasounds or computerized tomography (CT) scans for up to 2 years after treatment. Response duration was calculated from the

date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the Southwest Oncology Group (SWOG; Operations Office, San Antonio, TX) grading system (last revised 12/94), i.e., grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, and grade 5 = lethal/fatal. 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.

- *Patient Inclusion Criteria:* Presence of histologically confirmed unresectable HCC confined to the liver and at least one measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status 0-3; estimated life expectancy greater than 12 weeks; 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 within normal limits; bilirubin less than 1.5 x upper normal limit; serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase less than 5 x upper normal limit; normal pulmonary function defined as no more than 30% greater or less than the expected normal.
 - *Study Population and Treatment Administration:* Twenty-two patients were treated. Two patients were excluded from the efficacy analysis due to an unconfirmed diagnosis of HCC. Twenty patients received one TheraSphere® treatment; two patients received a second TheraSphere® treatment based on the principle investigator's discretion. Nine patients were classified as Okuda stage I and 11 patients as Okuda stage II. The median activity administered was 3.9 GBq (range, 2.0 GBq to 9.2 GBq). The median liver dose was 104 Gy (range, 46 Gy to 145 Gy).
 - *Safety Results:* One patient suffered from a possible angiography contrast agent allergic reaction that was judged by investigator to be severe in nature. All 22 treated patients reported at least one treatment-emergent adverse event; however, the majority (85%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening, or lethal/fatal) adverse events were liver related (45%) and gastrointestinal (19%). Liver toxicities were primarily elevated enzymes during the week after treatment. The gastrointestinal toxicities included three ulcers, one ileus, and one nausea. Three patients died during the follow-up period. The deaths were attributed to hepatitis (death approximately 5 months after TheraSphere® treatment; judged as possibly related to TheraSphere®), gastric ulcer (death approximately 2 months after TheraSphere® treatment; judged as probably related to TheraSphere®), and radiation pneumonitis (death approximately 2 months after TheraSphere® treatment; judged as definitely related to TheraSphere® after the patient received an estimated dose of 56 Gy to the lungs as a result of pulmonary shunting).
 - *Probable Benefit:* 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.
2. Pilot HCC [4] and Mixed Neoplasia Studies [3, 11]
- *Objectives:* The objectives of the Pilot HCC study were to define the activity of yttrium-90 microspheres administered by hepatic arterial infusion to patients with HCC and to evaluate the toxicity of yttrium-90 microsphere therapy. The objectives of the Mixed Neoplasia study were to evaluate the toxicity of yttrium-90 microsphere therapy and to define, using escalating radiation doses, the maximum tolerated dose of yttrium-90 glass microspheres administered by hepatic arterial infusion

that would be suitable for Phase II-III studies in a similar patient population.

- **Study Design:** Patients in the Pilot HCC study received TheraSphere® in an amount that was determined to deliver a radiation absorbed dose of approximately 50 Gy to the tumor. The Mixed Neoplasia study was designed to treat patients with metastatic colonic carcinoma of the liver, carcinoid tumor metastatic to the liver, or primary hepatobiliary carcinoma. Patients received a single injection of TheraSphere® with an initial group of patients receiving a calculated radiation absorbed dose of 50 Gy to the liver; after determination of acceptable and reversible toxicity, a second group of patients received 75 Gy to the liver followed by a third group of patients who received 100 Gy to the liver.

For both studies, response duration was calculated from the date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the SWOG grading system (see above under 100 Gy HCC Study).

- **Study Population and Treatment Administration:** Thirteen patients, nine from the Pilot HCC study and four from the Mixed Neoplasia study, provide safety data. All 13 patients were treated once with TheraSphere®. The median activity administered was 2.6 GBq (range, 2.2 GBq to 6.6 GBq). The median liver dose was 74 Gy (range, 34 Gy to 105 Gy). Because of the dose escalation, seven patients received less than 80 Gy.
- **Safety Results:** All 13 treated patients reported at least one treatment-emergent adverse event; however, the majority (82%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening, or lethal/fatal) adverse events were liver related (43%). Liver toxicities were primarily due to elevated enzymes during the week after treatment. Among the serious adverse events, two patients also experienced gastric ulcers. 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®).

• **Table 2. 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)

INDIVIDUALIZATION OF TREATMENT

1. Gastroduodenal ulceration is a potential complication of inadvertent disposition of radioactive microspheres. It is likely that inadvertent deposition of yttrium-90 microspheres in the terminal gastric vascular bed reflects the backflow of microspheres during administration or shunting through aberrant small vessels within the cirrhotic liver or tumor. Although angiographic occlusion techniques and the use of vasoactive drugs may reduce gastrointestinal shunting, their effectiveness is uncertain.
2. In some patients, part of the hepatic arterial blood supply bypasses the capillary bed and flows directly to the venous system. This may be associated with pathologic abnormalities of the liver. For such patients, a fraction F of spheres injected into the hepatic artery will not be embolized in the liver but will flow to the heart and subsequently be deposited into the lungs. As the product of the bypass fraction, F, and

the injected activity, A, increases the potential for delivering a damaging dose of radiation to the lungs increases. Consequently, it is essential that F be measured before use of this product. This can be done by injecting a tracer dose of Tc-99 MAA and observing with an Anger camera. The observed radiation from the lung field, divided by the total radiation observed by the camera is a measure of F. The product of F and A is then a measure of the activity that will be deposited into the lungs [22]. Based on clinical study experience [15, 16] with radioactive microspheres and TheraSphere® in HCC treatment, an upper limit of $F \times A$ of 610 MBq (16.5 mCi) is recommended. The estimated dose (Gy) to the lungs is equal to A (GBq) \times $F \times 50$, and assuming the total mass of both lungs to be 1 kg [23]; an upper limit of dose to the lungs from a single TheraSphere® treatment is 30 Gy.

INSTRUCTIONS FOR USE

Dosage and Administration

To correct for the physical decay of yttrium-90, the fractions that remain at selected time intervals from calibration are shown in Table 3.

Table 2
Yttrium-90 Physical Decay Table
Half-Life 64.2 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-4	1.044	26	0.755	56	0.546
-2	1.022	28	0.739	58	0.534
0*	1.000	30	0.723	60	0.523
2	0.979	32	0.708	62	0.511
4	0.958	34	0.692	64	0.500
6	0.937	36	0.677	66	0.489
8	0.917	38	0.663	68	0.479
10	0.897	40	0.649	70	0.469
12	0.878	42	0.635	72 (Day 3)	0.459
14	0.859	44	0.622	96 (Day 4)	0.354
16	0.841	46	0.609	120 (Day 5)	0.273
18	0.823	48 (Day 2)	0.596	144 (Day 6)	0.210
20	0.806	50	0.583	168 (Day 7)	0.162
22	0.789	52	0.570		
24 (Day 1)	0.772	54	0.558		

*Calibration Time

Preliminary Patient Evaluation

Prior to the administration of TheraSphere® the patient should undergo hepatic arterial catheterization using balloon catheterization or other appropriate angiographic techniques to prevent extrahepatic shunting [21]. Following the placement of the hepatic catheter 75 MBq to 150 MBq (2 mCi to 4 mCi) of Tc-99 MAA is administered into the hepatic artery to determine the extent of A-V shunting to the lungs. Air contrast scintigraphic views of the stomach are also obtained to confirm the absence of gastric and duodenal flow. If such flow is present and cannot be corrected using established angiographic techniques the patient is disqualified from treatment. When the possibility of extrahepatic shunting has been evaluated and the patient deemed acceptable for treatment, TheraSphere® can be administered.

Calculation of Dose

The recommended dose to the liver is between 80 Gy to 150 Gy (8,000 rad to 15,000 rad). The amount of radioactivity required to deliver the desired dose to the liver may be calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{Liver Mass (Kg)}]}{50 [1-F]}$$

where F is the fraction of injected activity deposited into the lungs as measured by Tc-99 MAA.

The liver volume and corresponding liver mass may be determined using CT or ultrasound scans.

If F is unknown, assume the upper limit of activity, which is 0.61 GBq, will be delivered to the lungs for the purpose of requisitioning TheraSphere®, and then using the Yttrium-90 Physical Decay Table (Table 3) to determine the appropriate time of injection. For determining the actual liver dose (Gy) delivered to the liver after injection, the following formula is used:

$$\text{Dose (Gy)} = 50 \frac{[\text{Injected Activity (GBq)}] [1 - F]}{\text{Liver Mass (Kg)}}$$

The upper limit of injected activity shunted to the lungs is $F \times A = 0.61 \text{ GBq}$.

TheraSphere® Administration Set

The TheraSphere® Administration Set (Table 4 and Diagram 1) consists of one dose vial inlet set, one dose vial outlet set and one empty vial. Both the inlet set and the outlet set are made up of preassembled sterile, apyrogenic components as shown in the schematic diagram.

The dose vial inlet set, used to connect the fluid source to the TheraSphere® dose vial, consists of a fluid line (3), an inlet line (7) and a 5 mL pumping syringe (6), joined together via a red 3-way stopcock (4). The red stopcock is used to switch from the fluid line to the inlet line, so that fluid may be drawn into the syringe, then pumped through the inlet line and into the TheraSphere® dose vial.

The piercing pin (2) at the free end of the fluid line is used to connect the inlet set to the fluid source (1), usually a heparinized (100 U/mL) saline solution. The 20-gauge needle (9) at the free end of the inlet line is used to connect the inlet set to the TheraSphere® dose vial (10). A check valve (8) prevents spheres from flowing back into the inlet line. Consequently, the inlet set should not contain any radioactivity during a normal procedure.

The dose vial outlet set, used to connect the TheraSphere® dose vial to the patient catheter, consists of an outlet line (13) and a vent line (17) joined together via a blue 3-way stopcock (14). The patient catheter is connected to the free port (15) on the blue stopcock. The blue stopcock is used to switch from the vent line to the catheter (16), so that the system's lines can be properly vented before the TheraSphere® dose is administered. The 20-gauge needle (12) at the free end of the outlet line is used to connect the outlet set to the TheraSphere® dose vial. The dispensing pin and filter vent assembly (18) at the end of the vent line is used to connect the outlet set to the sterile empty vial (19). The empty vial is used to collect fluid and any spheres that may flush through during air venting. The filter vent in the dispensing pin prevents pressure buildup in the empty vial and also blocks any spheres from escaping. The dose vial outlet set, including the empty vial, may contain radioactivity at the end of the administration procedure. For added safety, the lead pot (20) used for shipping may be used to hold the empty vial during the procedure.

Throughout the administration procedure, the TheraSphere® dose vial (10) remains sealed within the clear acrylic vial shield (11) in which it was supplied. A removable plug at the top of the vial shield provides access to the septum of the TheraSphere® dose vial.

Administration Instructions

The entire contents of the TheraSphere® dose vial are administered to the patient.

The directions for administration should be followed to ensure accurate delivery of the calculated dose. Approximately 96% of the radioactivity in the TheraSphere® dose vial will be delivered to the patient using the recommended technique.

Assembly of Dose Vial Inlet Set (Table 4 and Diagram 1)

1. The fluid line (3) is connected to the fluid source (1) via the white piercing pin (2).
2. The 5 mL syringe (6) is connected to the free port (5) on the red 3-way stopcock (4).
3. The red stopcock is switched to the fluid line.
4. 5 mL of solution is drawn into the syringe from the fluid source.
5. The tamper-evident seal is removed from the top of the clear acrylic vial shield (11) exposing the top shielding plug which the seal had secured in place. The plug is now free and is removed by turning the vial shield over adhering to appropriate radiation safety procedures.
6. Once the plug has been removed, the vial shield is returned to its upright position and the septum of the TheraSphere® dose vial (10) is swabbed with alcohol.
7. The 20-gauge needle (9) at the free end of the inlet line (7) is carefully inserted through the center of the TheraSphere® dose vial septum and pushed to the bottom of the vee at the base of the vial.

Assembly of Dose Vial Outlet Set (Table 4 and Diagram 1)

8. The flip-off seal is removed from the empty vial (19).
9. The dispensing pin and filter vent assembly (18) on the free end of the vent line (17) is inserted through the septum of the empty vial.
10. The empty vial is placed in the lead pot used for shipping (20).
11. The 20-gauge needle (12) at the free end of the outlet line (13) is carefully pushed through the septum of the TheraSphere® dose vial until it is just visible below the level of the seal.

System Evacuation (Table 3 and Diagram 1)

12. The red stopcock is switched to the inlet line.
13. The blue stopcock (14) is switched to the vent line.
14. Fluid from the syringe is slowly forced through the inlet line, into the TheraSphere® dose vial, and out through the outlet and vent lines until all air is exhausted from the system and fluid has entered the empty vial.
NOTE: A low flow rate and gentle tapping of the TheraSphere® dose vial will reduce the possibility of premature introduction of spheres into the outlet line.

15. The outlet needle is pushed half way into the TheraSphere® dose vial. The purpose of this step is to eliminate the possibility of sweeping air that may be trapped near the top of the TheraSphere® dose vial into the catheter.
16. The red stopcock is switched to the fluid line and the syringe is refilled with 5 mL of solution.
17. The red stopcock is switched back to the inlet line.

TheraSphere® Administration (Table 4 and Diagram 1)

18. The patient catheter (16) is attached to the free port (15) on the blue stopcock.
19. The blue stopcock is switched to the catheter.
20. After verifying that both stopcocks are correctly positioned, the fluid in the syringe is expressed at a rate of approximately 1 mL per second. This flow rate will carry the spheres out of the TheraSphere® dose vial, through the outlet line, and into the catheter.
21. The red stopcock is switched to the fluid line and the syringe is refilled with 5 mL of solution.
22. The red stopcock is switched back to the inlet line and another 5 mL of solution is administered as in step 19.

Disassembly (Table 4 and Diagram 1)

23. The blue stopcock is switched to the vent line.
24. The catheter is disconnected from the blue stopcock.
25. The rest of the administration set is disassembled. The empty TheraSphere® dose vial, the dose vial outlet set and the catheter should be stored for decay or disposed of as radioactive waste.

RADIATION DOSIMETRY

The yttrium-90 in TheraSphere® is a constituent of an insoluble matrix thereby limiting irradiation to the immediate vicinity of the spheres. The average range of the radiation in tissue is 2.5 mm. One GBq (27 mCi) of yttrium-90 per kg of tissue gives an initial radiation dose of 13 Gy (1,297 rad) per day. The mean life of yttrium-90 is 3.85 days; thus, the radiation dose delivered by yttrium-90 over complete radioactive decay starting at an activity level of 1 GBq (27 mCi) per kg is 50 Gy (5,000 rad).

HOW SUPPLIED

TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi), and 20 GBq (540 mCi). The dose is supplied in 0.05 mL of sterile, pyrogen-free water in a vee-bottom vial sealed within a 12 mm clear acrylic vial shield. Each dose is supplied with all the components required for administration, exclusive of items utilized in catheterization. The TheraSphere® dose and Administration Set should be stored at room temperature.

DISTRIBUTION

TheraSphere® is manufactured and distributed by MDS Nordion Inc., Kanata, Ontario, Canada.

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Table 4
TheraSphere® Administration Set Configuration

Drawing Number	Item
1	Fluid source
2	Piercing pin
3	Fluid line
4	Red 3-way stopcock
5	Free port on the red 3-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 3-way stopcock
15	Free port on the blue stopcock
16	Catheter
17	Vent line
18	Filter vent assembly
19	Sterile empty vial
20	Lead pot

Diagram 1
TheraSphere® Administration Set Configuration

