TheraSphere™
Yttrium-90 Glass Microsphere System

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℞ ONLY

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

REUSE WARNING

Reuse, reprocessing or resterilization of sterile, single use components may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

DEVICE DESCRIPTION

The TheraSphere Yttrium-90 (Y-90) Glass Microsphere System consists of:

- a sterile, single use, dose vial of TheraSphere, Y-90 Glass Microspheres, available in 3 gigabecquerel (GBq) – 20 GBq dose sizes in 0.5 GBq increments (81 mCi (milliCurie) – 540 mCi dose sizes in 13.5 mCi increments);
- a sterile, single-use TheraSphere Administration Set; and
- a non-sterile, re-usable TheraSphere Administration Accessory Kit.

Contents

Quantity	Description
1	TheraSphere Yttrium-90 Glass Microspheres Dose Vial

The TheraSphere Microspheres are delivered into the liver tumor through a microcatheter placed into the hepatic artery that supplies blood to the tumor. When infused, the TheraSphere Microspheres are distributed based on regional blood flow. Due to the particle size, they are unable to pass through the liver arteriolar capillary and thus become trapped in the tumor vasculature. Once delivered, the beta radiation emitted by Y-90 exerts a local radiotherapeutic effect distributed in proportion to blood flow to the perfused area, including the tumor with some concurrent Y-90 radiation to surrounding normal liver tissue within the perfused liver volume. The radiation emitted by the glass microspheres diminishes significantly over approximately 2 weeks post treatment; however, the glass microspheres remain permanently implanted in the liver tissue.

The TheraSphere Administration Set enables delivery of the TheraSphere Microspheres from the dose vial to the microcatheter and into the hepatic artery. Figure 1 is a schematic of the Administration Set. The TheraSphere Administration Set is a sterile assembly of tubing, a needle plunger assembly, a 20 mL syringe, and an empty sterile vial. The TheraSphere Administration Set is used to connect the TheraSphere Microspheres dose vial to a microcatheter, while assembled with the TheraSphere Administration Accessory Kit, forming the TheraSphere Administration System.

The one-way valves incorporated in the Administration Set control the flow of liquid such that it will only flow in the appropriate direction. Pulling back on the syringe plunger will fill the syringe from the fluid source. Pushing the syringe plunger will move fluid toward the needle plunger assembly. Prior to the administration of the microspheres, the Administration Set is manually primed by pushing the sterile flushing solution through the set to purge air from the lines.

The TheraSphere Administration Accessory Kit ensures optimal layout of the Administration Set and dose vial. Figure 2 is a drawing of the Administration Accessory Kit. The TheraSphere Administration Accessory Kit is intended to aid in positioning the TheraSphere Administration Set for the efficient transfer of TheraSphere Microspheres to the patient, and to provide radiation shielding and containment. The TheraSphere Administration Accessory Kit contains reusable components including an acrylic box base unit, removable top shield, removable side shield, catheter holder - extension arm, and bag hook.

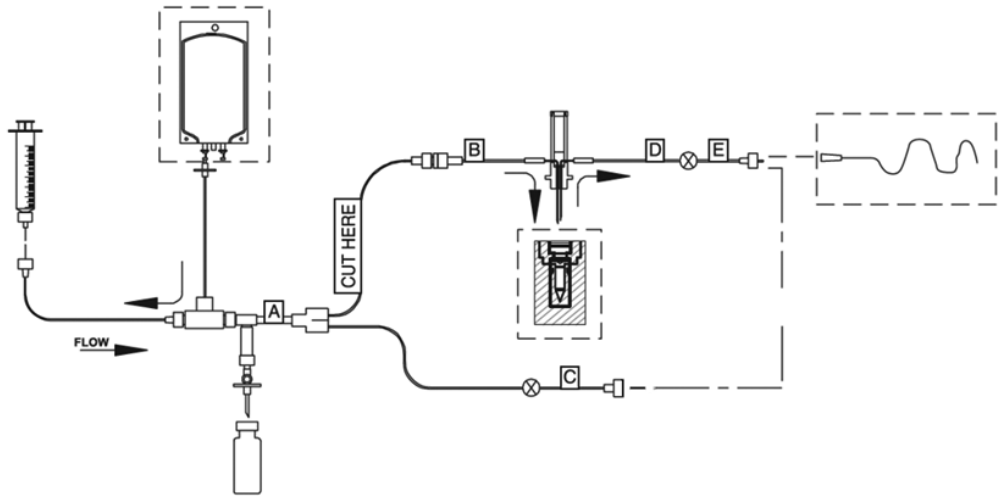

Figure 1. TheraSphere Administration Set

(Items in dashed boxes are not supplied with the Administration Set)

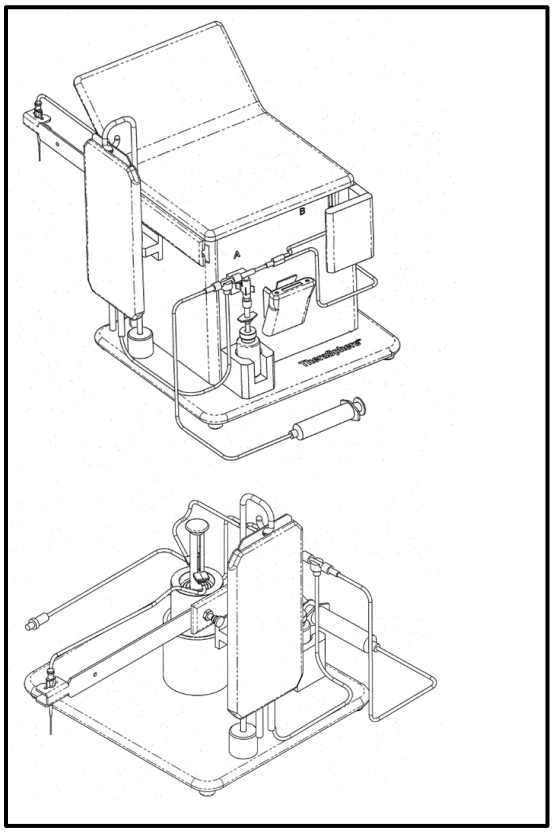

Figure 2. TheraSphere Administration Accessory Kit

(Shown assembled with TheraSphere Administration Set)

Materials

The TheraSphere Microspheres consist of a blend of Aluminum Oxide, Silicon Dioxide and Yttrium Oxide (as shown in Table 1), where a portion of the Yttrium (Y) is the isotope Y-90. The radioactive microspheres are supplied in 0.6 mL pyrogen-free water. The Y-90 decays to the stable isotope zirconium-90 (Zr-90).

Table 1: Composition of Glass Microspheres

Microsphere Component	Composition by Weight
Aluminum Oxide (Al_2O_3)	20 %
Silicon Dioxide (SiO_2)	40 %
Yttrium Oxide (Y_2O_3)	40 %

Magnetic Resonance Imaging Safety Information

TheraSphere Microspheres are Magnetic Resonance (MR) safe.

Radiation

The average range of the radiation within the tissue is 2.5 mm. One GBq (27 mCi) of Y-90 per kg (kilogram) of tissue gives an initial radiation dose of 13 Gy (Gray) (1297 rad) per day. The mean life of Y-90 is 3.85 days and thus, the radiation dose delivered by Y-90 over complete radioactive decay of 1 GBq (27 mCi) per kg is 50 Gy (5000 rad). The radioactive properties of Y-90 are shown in Table 2.

[See ***Handling and Storage*** for Radiation Safety Information]

Table 2: Yttrium-90 Radioactive Properties

Decay Product	Zirconium-90
Half-Life, t ½	64.1 hours (2.67 days)
Average range of beta radiation in tissue	2.5 mm (0.1 in)
Initial radiation dose for 27 mCi (1 GBq) of Y-90 administered to 1 kg (2.2 lb) of liver tissue	13 Gy / day (1297 rad / day)
Mean Life	3.85 days
Radiation dose delivered to 2.2 lb (1 kg) of tissue from complete radioactive decay of 1 GBq (27 mCi) of Y-90	13 Gy x 3.85 days = 50 Gy (5000 rad)

User Information

Administration of radioactive Y-90 microspheres requires expertise in hepatic vascular anatomy as well as angiographic, nuclear medicine, and radiographic procedures. Due to the technical expertise required for these various procedures for treatment (patient selection, work-up, treatment, and post-procedure surveillance), a multi-disciplinary approach including health care professionals qualified in Nuclear Medicine, Medical Oncology, Hepato-gastroenterology, Interventional Radiology, Radiology and Radiation Oncology is recommended. The site must have the appropriate facilities, equipment, licenses and approvals to administer TheraSphere Microspheres according to local regulations and authorities.

Users and personnel participating in the use of the device should have appropriate training and be experienced with the administration of Y-90 microspheres prior to the unsupervised use of TheraSphere Microspheres. New site training is offered by Boston Scientific.

Initial patient cases may be supervised by a representative of Boston Scientific for sites/users new to the administration of Y-90 microspheres. Additional onsite support is available, upon request.

INDICATIONS FOR USE

TheraSphere Microspheres are indicated for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm diameter), in patients with unresectable hepatocellular carcinoma (HCC), Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status.

CONTRAINDICATIONS

TheraSphere Microspheres are contraindicated in patients:

- whose Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques.
- who show shunting of blood to the lungs that could result in delivery of greater than 0.61 GBq (16.5 mCi) to the lungs. Radiation pneumonitis has been seen rarely 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 or bleeding diathesis.
- who have pulmonary insufficiency (conventionally defined by an arterial oxygen pressure (Pa,O_2) of < 60 mmHg, or oxygen saturation (Sa,O_2) of < 90 %).
- with portal vein thrombosis (PVT) Type 4 involvement and lack of Tc-99m MAA deposition on the PVT seen on the Tc-99m MAA imaging.
- with > 70 % tumor replacement in the liver.
- who have severe liver dysfunction, including hepatic encephalopathy, clinically evident ascites, or treatment with diuretics for ascites.
- with comorbidities or poor overall health (e.g., Eastern Cooperative Oncology Group (ECOG) performance status rating > 2) which may make the patient a poor candidate for locoregional radiation treatment.
- who are pregnant.

WARNINGS

The following pre-treatment, high-risk factors (disease characteristics) have been associated with serious adverse events deemed possibly related to use of the device:

- infiltrative tumor type
- tumor nodules too numerous to count
- AST or ALT > 5 times ULN
- bilirubin > 2 mg/dL
- tumor volume > 50% combined with albumin < 3 g/dL

Limited Radiation Dosimetry Planning Precision

The amount of radiation delivered to HCC targets has been found to differ compared to the amount planned *[see **DOSISPHERE Radiation Dosimetry Planning Precision**]*. Similar levels of precision should not be assumed when planning for Y-90 microsphere radiation therapy compared to when planning for external beam radiation therapy. [*See **Dosing and Administration Instructions***]

Procedural

- It is important to avoid any aggressive arterial procedure that may lead to arterial spasm that impairs TheraSphere Microspheres distribution in the perfused liver target volume and may lead to underdosing or non-target deposition of TheraSphere Microspheres.

Radiation Safety

- Keep the TheraSphere Microspheres dose vial upright and stored in its lead pot before and during patient treatment, except as required for radiation measurement. Failure to do so could cause radiation exposure or damage to the product. Do not open the dose vial acrylic shield prior to patient treatment.
- Beta radiation from the tubing and exposed microcatheter is highest during microsphere transfer. Stand behind shielding and/or maintain distance.
- Post-treatment, waste materials require caution to prevent contamination and beta shielding due to residual glass microspheres. [See ***Cleanup of Administration System***]
- As in the use of any radioactive material, ensure minimum radiation exposure to the patient unrelated to the therapeutic objective, and minimize radiation exposure to workers and others in contact with the patient.

PRECAUTIONS

Patients with Impaired Liver Function

- No efficacy or safety data from the LEGACY, DOSISPHERE or TARGET studies are available to support the use of the device in patients with Child-Pugh C cirrhosis.

Procedural

- Two needles are located inside injector assembly. When removing the cap from the needle injector assembly, follow standard sharps procedure.

Release and Post-Treatment

- Use universal precautions for body fluid contact. Trace Y-90 may be detectable in blood and urine; handle with gloves and dispose as normal body fluids. The radiation field is expected to be less than 10 µSv/h (1 mrem/h) at 1 m (3 ft) from the patient's abdomen. Supplemental shielding and segregation of the patient are not required to maintain exposure to others below regulated limits.
- The patient should follow good hygiene (e.g., proper hand washing). Caregivers, family, and others do not require restrictions on patient contact; however, they can minimize their radiation exposure by avoiding prolonged time (>12 hours per day) within 0.3 m (1 ft) of the patient's abdomen for the first week post therapy. Patients should be advised that radiation emitted from the patient may be detectible at security screening.
- If the patient requires hospitalization, surgery, medical assessment or treatment regarding any part of their thorax or abdomen within first 2 weeks of treatment, the patient should advise the hospital and treating physician of the TheraSphere Microspheres implant. The physician should consult their radiation safety staff for handling and disposal of liver tissue.
- Special liver tissue handling may be required for post-treatment surgery, explant, or transplant since the glass microspheres remain permanently implanted in the liver tissue. Disclosure of the treatment will be required if cremation is considered.
- See ***Release and Post-Procedure*** for more information.

Vulnerable Patients

- No effectiveness or safety data are available to support the use of the device in children or breast-feeding women.

ADVERSE EVENTS

The use of this product leads to irradiation of both tumorous and normal liver tissue. As a result, patients with compromised liver function may be at greater risk of liver function impairment and hence could experience complications. [See ***Warnings*** for more information]

Potential adverse events which may be associated with the use of TheraSphere Microspheres in the treatment of hepatocellular carcinoma usually occur within the first 4 to 6 weeks after treatment.

Based on clinical trial data, literature reviews and post market surveillance, adverse events potentially associated with treatment using Y-90 microspheres, including TheraSphere Microspheres, may include the following:

- Allergic reaction (contrast or other)
- Anorexia
- Arrhythmia (e.g. supraventricular arrhythmia)
- Ascites
- Aspiration pneumonia (procedure related)
- Bile duct injury
- Bleeding/hemorrhage
- Chills/rigors
- Cholangitis
- Cholecystitis
- Cognitive changes (i.e. mood alteration, anxiety)
- Colitis
- Death

- Dehydration
- Dizziness
- Edema including pulmonary edema
- Electrolyte abnormalities
- Fall
- Fatigue/muscle weakness
- Fever
- Flushing (procedure related)
- Gastrointestinal bleeding
- Gastrointestinal symptoms (e.g. abdominal distention, constipation, diarrhea, nausea, vomiting)
- Gastrointestinal ulcer or ulceration
- Hematological cytopenia (e.g. anemia, lymphopenia, neutropenia, thrombocytopenia)
- Hematoma
- Hepatic dysfunction
- Hepatic encephalopathy
- Hepatic failure
- Hiccups
- Hypertension
- Hypotension
- Infection/abscess/sepsis
- Malaise
- Need for additional intervention or surgery
- Nerve damage (procedure related)
- Pain/discomfort
- Pleural effusion
- Portal hypertension
- Post-embolization syndrome (PES)
- Pulmonary Fibrosis
- Radiation exposure (unintended)
- Radiation induced disease (i.e. fibrosis, gastritis, esophagitis, pneumonitis, pancreatitis, ulceration)
- Radio Embolization Induced Liver Disease (REILD)
- Renal insufficiency/failure (elevated BUN/creatinine)
- Respiratory distress/insufficiency/failure/dyspnea
- Thrombosis/thrombus
- Tumor inflammation including tumor edema
- Tumor lysis syndrome
- Vessel trauma (e.g. dissection, injury, pseudoaneurysm, perforation, rupture)
- Weight loss

CLINICAL STUDIES

LEGACY

EVALUATION OF SAFETY IN THE LEGACY STUDY

The safety of TheraSphere Microspheres was evaluated in the LEGACY study, a retrospective, single-arm, multi-center study in 162 patients with a single, unresectable HCC tumor measuring 1 cm - 8 cm at the greatest diameter. Of the 162 patients, 32 patients (19.8 %) received two or more TheraSphere Microspheres treatments. Safety data were collected via a retrospective review of data in the patients' medical records. For every patient file, one site's investigator reviewed the files and retrospectively documented adverse events (AEs) and serious adverse events (SAEs) that occurred during the follow-up period and determined the severity and the causality. Serious adverse events occurred in 16 patients (10 %). Serious adverse events that occurred in more than one patient were vomiting and pneumonia (n=3 in each, 1.9 % each), and abdominal pain, ascites and nausea, (n=2 in each; 1.2 % each). One (0.6 %) fatal adverse event occurred in patients who received TheraSphere Microspheres: cerebral vascular accident; the death occurred 173 days after initiation of TheraSphere Microspheres and 66 days after the last dose of TheraSphere Microspheres.

BSC assesses this event as not related to the TheraSphere Microspheres treatment and pre-treatment imaging procedures. Table 3 summarizes the adverse events in patients in the LEGACY study.

Table 3: Adverse Events Occurring in ≥ 5 % of Patients with HCC in LEGACY

Adverse Event	All Grades N=162 n (%)	Grades 3-4 N=162 n (%)
General Disorders		
Fatigue[a]	56 (34.6)	1 (0.6)
Blood and Lymphatic System Disorders		
Lymphocyte count decreased	46 (28.4)	12 (7.4)
White blood cell count decreased	21 (13.0)	1 (0.6)
Platelet count decreased	19 (11.7)	2 (1.2)
Hepatobiliary and Gastrointestinal Disorders		
Blood bilirubin increased[b]	29 (17.9)	3 (1.9)
Blood alkaline phosphatase increased	14 (8.6)	0
AST increased	11 (6.8)	0
Abdominal pain[c]	34 (21.0)	2 (1.2)
Nausea	28 (17.3)	2 (1.2)
Ascites	13 (8.0)	3 (1.9)
Vomiting	13 (8.0)	3 (1.9)
Decreased appetite	13 (8.0)	0
Constipation	9 (5.6)	0
Metabolism and Nutrition Disorders		
Hypoalbuminemia	14 (8.6)	1 (0.6)
Hyperglycemia	11 (6.8)	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	9 (5.6)	2 (1.2)

[a]Includes asthenia

[b]Includes hyperbilirubinemia

[c]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, and epigastric discomfort

[d]Includes back pain, myalgia, neck pain, and pain in extremity

Related AEs

Eighty percent (129/162) of patients had one or more AE assessed as at least possibly related to TheraSphere Microspheres or the treatment procedure, including 62 % of patients in the Treated Population with AEs assessed as at least possibly related to TheraSphere Microspheres, and 45 % of patients with AEs assessed as at least possibly related to the treatment procedure. The AEs related to TheraSphere Microspheres or the treatment procedure that occurred in ≥ 5 % of patients were similar to the most common AEs overall as described in Table 4.

Table 4: Related Adverse Events Occurring in ≥ 5 % of Patients with HCC in LEGACY

Adverse Event	All Grades, N=162, n (%)	Grades 3-4, N=162, n (%)
General Disorders		
Fatigue[a]	54 (33.3)	1 (0.6)
Blood and Lymphatic System Disorders		
Lymphocyte count decreased	46 (28.4)	12 (7.4)
White blood cell count decreased	16 (9.9)	1 (0.6)
Platelet count decreased	14 (8.6)	2 (1.2)
Hepatobiliary and Gastrointestinal Disorders		
Blood bilirubin increased[b]	24 (14.8)	2 (1.2)
Blood alkaline phosphatase increased	14 (8.6)	0
AST increased	10 (6.2)	0

Abdominal pain[c]	29 (17.9)	2 (1.2)
Nausea	24 (14.8)	2 (1.2)
Ascites	10 (6.2)	2 (1.2)
Vomiting	11 (6.8)	3 (1.9)
Decreased appetite	11 (6.8)	0
Metabolism and Nutrition Disorders		
Hypoalbuminemia	9 (5.6)	0

[a]Includes asthenia

[b]Includes hyperbilirubinemia

[c]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, and epigastric discomfort

AEs related to dose

A dosimetry analysis showed no statistically significant impact of any baseline covariate on the occurrence of SAEs or Grade ≥ 3 AEs assessed as at least possibly related to TheraSphere Microspheres or the treatment procedure.

AEs in specific populations

In the 109 patients with low baseline platelet counts and/or high baseline INR values, 9 patients had a bleeding event; these included 1 SAE (gastrointestinal hemorrhage) and 8 non-serious events.

In 38 patients with low baseline white blood cell count values, 3 patients had an infection event; these included 1 SAE (lung infection) and 2 non-serious events.

EFFECTIVENESS OF THERASPHERE MICROSPHERES IN THE LEGACY STUDY

LEGACY STUDY: DESIGN, ENDPOINTS AND PATIENT CHARACTERISTICS

LEGACY was a retrospective, single-arm, multi-center study in adult patients with a single, unresectable HCC tumor measuring 1 cm - 8 cm at the greatest diameter. Patients were required to have a confirmed (by histology or imaging) solitary, unresectable HCC of any etiology, tumor measurable by mRECIST, Child-Pugh A cirrhosis, and Barcelona Clinic Liver Cancer (BCLC) A disease with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or BCLC C disease with ECOG PS of 1. The patients must have received lobar or selective (no more than 2 segments) TheraSphere administration with a lobar absorbed dose of up to 180 Gy, had contrast-enhanced diagnostic imaging within 60 days prior to TheraSphere administration (or, if >60 days before TheraSphere, confirmatory imaging at the time of angiography), and had follow-up contrast-enhanced imaging. The study excluded patients who had prior therapy for HCC, any vascular invasion, clinically evident ascites or on diuretics for ascites, hepatic encephalopathy, extrahepatic metastases, and a synchronous diagnosis of additional malignancy besides HCC.

Patients were identified through retrospective chart review at three sites in the U.S. and all consecutively treated patients (from 01/01/2014 through 12/31/2017 inclusive) who met all study eligibility criteria were included in the study. The study data were collected as part of usual patient care at each participating institution. Patients were expected to have imaging for tumor assessment available for the Month 3 or Month 4 time point (depending on institutional clinical practice) after the initial post-TheraSphere Microspheres treatment visit, and thereafter at three-month intervals through 12 months, at six-month intervals at 18 months and 24 months, and at 12-month intervals thereafter. Patients were followed until they met protocol-specified criteria for the end of clinical data collection (i.e., receipt of a non-TheraSphere Microspheres treatment for HCC in the initial TheraSphere Microspheres treatment area, death, loss to follow-up) or reached the end of the study on 12/31/2018.

A total of 343 patients were screened, and 162 patients were enrolled and included in the analysis of safety and effectiveness of TheraSphere Microspheres in this study. The median age was 66 years (range: 21 - 90), 43 % were < 65 years, 57 % were ≥ 65 years, 76 % were male, 49 % were White, 10 % were Black, and 8 % were Asian. The etiology for HCC was hepatitis C in 69%, alcoholic liver disease in 30%, non-alcoholic steatohepatitis in 14 %, and hepatitis B in 9 %. Child-Pugh score A5 was 67 % and A6 was 33 %. BCLC A (ECOG PS 0) was 60 % and BCLC C (ECOG PS 1) was 40 %. The LEGACY study did not evaluate safety and effectiveness in patients with the following characteristics: any vascular invasion or Child-Pugh score B or C or prior systemic therapy.

The primary and secondary effectiveness endpoints were evaluated based on a single TheraSphere Microspheres administration. Of the 162 patients in the Treated Population, 32 patients (19.8 %) received two or more TheraSphere Microspheres treatments and 14 of these patients received a second TheraSphere Microspheres treatment to complete the treatment of baseline disease within 6 months from first treatment.

PRIMARY EFFECTIVENESS ENDPOINT RESULTS

Effectiveness results are based on a median duration of follow-up from first TheraSphere Microspheres treatment of 29.9 months. Local tumor control was demonstrated by the results below:

- ORR by localized mRECIST was 72.2 % (95 % CI: 64.9, 78.5);
- DOR by localized mRECIST was ≥ 6 months in 76.1 % of responders;
- ORR was 68.5 % and the DOR was ≥ 6 months in 74.8 % of responders by mRECIST;
- ORR was 46.3 % and the DOR was ≥ 6 months in 72.0 % of responders by RECIST 1.1.

Effectiveness results are summarized in Table.

Table 5: Objective Response Rate (ORR) and Duration of Response (DOR), LEGACY Study

	Treated Population N=162		
	Localized mRECIST	**mRECIST**	**RECIST 1.1**
ORR per BICR, n (%)	117 (72.2 %)	111 (68.5 %)	75 (46.3 %)
(95 % CI)[a]	(64.9, 78.5)	(61.0, 75.2)	(38.8, 54.0)
Complete Response (CR)	115 (71.0 %)	109 (67.3 %)	11 (6.8 %)
Partial Response (PR)	2 (1.2 %)	2 (1.2 %)	64 (39.5 %)
DOR per BICR			
Range (months)[b,c]	1.5*, 48.1*	1.5*, 48.1*	1.5*, 45.1*
Percent with duration ≥ 6 months[d]	76.1 %	74.8 %	72.0 %

* Indicates response was ongoing at the time stated
[a] 95 % CI for percentage of patients with ORR per BICR, based on the methodology of Wilson (1927)
[b] Months = (Date of first PD - Date of first CR or PR + 1)/30.4375. If no PD occurred, the date of the last imaging assessment within the treatment area, before any further HCC treatment was administered, was used.
[c] Median duration of response by Kaplan Meier analysis not reached with a median follow-up duration of approximately 30 months.
[d] Percents are based on the number of patients with confirmed CR or PR.

Note: Localized mRECIST is defined as mRECIST assessment within the treatment area, including the entirety of any tumor that is either partially or completely within the treatment area; the treatment area is the perfused volume infused with TheraSphere Microspheres. Responses are defined as a patient with CR or PR that is confirmed at a subsequent visit > 4 weeks (30 days) after the date of the first occurrence of CR or PR. Any assessments performed subsequent to the administration of any further HCC treatment within the initial TheraSphere Microspheres treatment area are excluded. Patients who received non-TheraSphere Microspheres treatment outside of the initial treatment areas before the confirmatory scan for response assessment was performed are not excluded from the mRECIST (N=2) and RECIST 1.1 (N=4) analysis.

Abbreviations: BICR: blinded independent central review; CI: confidence interval; mRECIST: modified Response Evaluation Criteria in Solid Tumors; PD: progressive disease

There is no evidence supporting the use of systemic therapy in combination with TheraSphere Microspheres.

USE IN THE GERIATRIC POPULATION

The LEGACY study included 64 (40 %) patients 65 to < 75 years of age and 29 (18 %) patients ≥ 75 years of age. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

DOSIMETRY

Perfused liver volume was determined by post Y-90 SPECT/CT bremsstrahlung (N=51) and/or CBCT diagnostic (N=104) imaging and was unique for each patient within the LEGACY study. In seven patients, the perfused liver volume was not evaluable.

Table 6 provides the median perfused liver volume and median absorbed dose to perfused liver volume (Gy) by perfused liver volume quartiles. Patients with a subsegmental or segmental perfused liver volume (up to two segments) were within the 1st to 3rd quartiles, while the 4th quartile contained both segmental (N=27) and lobar perfused volumes (N=11). The median perfused liver volume and absorbed dose to perfused liver volume for the full cohort are also listed in Table 6.

Table 6: Perfused Liver Volume (cm^3) and Absorbed Dose to Perfused Liver Volume (Gy) by Quartile and Full Cohort

	1st Quartile (N=39)	2nd Quartile (N=39)	3rd Quartile (N=39)	4th Quartile (N=38)	Full Cohort (N=155)
Perfused liver volume (cm^3) Median (Range)	62 (19 - 91)	121 (92 - 155)	200 (158 - 262)	459.5 (271 - 1363)	155.0 (19 - 1363)
Absorbed dose to perfused liver volume (Gy) Median (Range)	927 (188 - 2980)	518 (147 - 1313)	410 (122 - 1025)	146 (70 - 396)	410.1 (70 - 2980)

Note: Seven patients did not have an absorbed dose to perfused volume.

HISTOPATHOLOGIC ANALYSIS

Histopathologic analysis to determine degree of necrosis was evaluated by individual institutions for patients who underwent transplant or resection (N=45) following TheraSphere Microspheres treatment. A total of 20 patients underwent transplant or resection prior to objective response assessment (N=11) or prior to confirmation of objective response (N=9). Table summarizes the histopathologic response for patients who achieved a complete response by objective response assessment in those patients that underwent a transplant or resection.

Table 7: Histopathology Response

Imaging Response	Histopathology Response
CR (N=25)	Complete (N=16)
	Extensive (N=6)
	Partial (N=3)

Abbreviation: CR: Complete Response

Note: Degree of Necrosis, as determined by site investigators: Complete = 100 % necrosis (no viable tumor); Extensive = 50-99 % necrosis (significant necrosis with presence of minimal viable tissue); Partial = minimal necrosis (encompassing < 50 % of the treated tumor).

DOSISPHERE

DOSISPHERE Study: Design, Patient Characteristics and Endpoints

DOSISPHERE compared the safety and efficacy of TheraSphere Microspheres in patients with unresectable HCC, using multicompartment dosimetry (MCD) versus single compartment dosimetry (SCD). Multiple commercial dosimetry software tools were used for investigator assessment and Simplicit90Y was used for central and Independent Review Committee (IRC) assessment. The dosimetry goal for patients in the MCD arm was a tumor absorbed dose (TAD) ≥205 Gy (≥300 Gy where feasible), while keeping the normal perfused liver dose <120 Gy if the hepatic reserve[1] was 30%. A higher perfused NTAD was allowed if the hepatic reserve was >30%. The dosimetry goal for patients in the SCD arm was to deliver a perfused liver volume absorbed dose of 120 ± 20 Gy. Patients were eligible if they had at least one tumor ≥7 cm with or without PVT, Child-Pugh stage A (or B7 if bilirubin <35 µmol/L), BCLC classification A, B or C, and hepatic functional

[1] Hepatic reserve is the fraction of functional liver that will not receive Y-90.

reserve ≥30%. The primary endpoint was ORR in the index lesion at month 3 post-treatment per European Association for the Study of the Liver (EASL) criteria. A total of 60 patients were randomized (intention to treat [ITT] population). Of these, 56 patients (93.3%) received treatment and constituted the modified ITT [mITT] population, with 28 patients assigned to each arm. Baseline characteristics are summarized in Table 8.

Table 8: DOSISPHERE study baseline characteristics, mITT Population (Treated Patients)

Baseline Characteristics	**mITT population** (Treated patients)	
	MCD (N = 28)	**SCD (N = 28)**
Age (years); Median (Range)	65.5 (39-86)	63.0 (18-84)
Child Pugh A5 / A6-B7, n (%)	22 (78.6) / 6 (21.4)	22 (78.6) / 6 (21.4)
BCLC B / C, n (%)	3 (10.7) / 25 (89.3)	2 (7.1) / 26 (92.9)
Portal vein invasion, n (%)	18 (64.3)	21 (75.0)
HCC Solitary / Multifocal, n (%)	15 (53.6) / 13 (46.4)	12 (42.9) / 16 (57.1)
Tumoral involvement (%); Mean ± STD	23.01 ± 13.96	25.69 ± 14.19
Index tumor size (cm); Mean ± STD	10.36 ± 2.44	10.67 ± 2.79

Abbreviations: BCLC: Barcelona Clinic Liver Cancer, HCC: hepatocellular carcinoma, (m)ITT: (modified) intent-to-treat; MCD: multicompartment dosimetry; SCD: single compartment dosimetry, STD: standard deviation

From the full DOSISPHERE study population (28 patients in each arm), only one patient in each arm met the current labeling indication.

Evaluation of Safety in the DOSISPHERE Study

The proportion of patients experiencing at least one treatment-emergent adverse event (TEAE) was comparable between the two treatment arms (26/28, 92.9% in the MCD arm and 24/28, 85.7% in the SCD arm). Among the 277 TEAEs, 129 (46.5%) were assessed as treatment related. Table 9 and Table 10 summarize the most commonly reported related TEAEs (≥5%) of any severity grade and all reported treatment emergent SAEs, respectively.

As the percentage of liver treated increases, the rate and severity of TheraSphere Microspheres related TEAEs may increase, mainly lymphopenia, abdominal pain, fatigue/asthenia, ascites, and bilirubin increase (including hyperbilirubinemia and jaundice).

Post-treatment follow-up data in the DOSISPHERE study was limited by the majority of patients discontinuing the study after the Month 3 visit. Thus, delayed adverse events might not have been detected.

Table 9: Summary of Related TEAEs Occurring in ≥ 5% of Patients (mITT population)

	MCD (N=28)		**SCD (N=28)**		**Total (N=56)**	
	All Grades (N=16) n (%)	**Grades ≥3 (N=12) n (%)**	**All Grades (N=19) n (%)**	**Grades ≥3 (N=12) n (%)**	**All Grades (N=35) n (%)**	**Grades ≥3 (N=24) n (%)**
Blood and lymphatic system disorders						
Lymphopenia	10 (35.7)	9 (32.1)	8 (28.6)	7 (25.0)	18 (32.1)	16 (28.6)
Thrombocytopenia	1 (3.6)	0	3 (10.7)	0	4 (7.1)	0
Gastrointestinal disorders						
Abdominal pain	2 (7.1)	0	1 (3.6)	0	3 (5.4)	0

	MCD (N=28)		**SCD (N=28)**		**Total (N=56)**	
	All Grades (N=16) n (%)	**Grades ≥3 (N=12) n (%)**	**All Grades (N=19) n (%)**	**Grades ≥3 (N=12) n (%)**	**All Grades (N=35) n (%)**	**Grades ≥3 (N=24) n (%)**
Abdominal pain upper	2 (7.1)	0	1 (3.6)	0	3 (5.4)	0
Ascites	2 (7.1)	1 (3.6)	5 (17.9)	1 (3.6)	7 (12.5)	2 (3.6)
Nausea	5 (17.9)	0	2 (7.1)	0	7 (12.5)	0
General disorders and administration site conditions						
Asthenia	4 (14.3)	1 (3.6)	4 (14.3)	0	8 (14.3)	1 (1.8)
Fatigue	4 (14.3)	0	2 (7.1)	1 (3.6)	6 (10.7)	1 (1.8)
Hepatobiliary disorders						
Hepatic failure	2 (7.1)	1 (3.6)	1 (3.6)	1 (3.6)	3 (5.4)	2 (3.6)
Jaundice	0	0	3 (10.7)	1 (3.6)	3 (5.4)	1 (1.8)
Investigations						
Blood bilirubin increased	2 (7.1)	1 (3.6)	2 (7.1)	0	4 (7.1)	1 (1.8)
Lymphocyte count decreased	3 (10.7)	1 (3.6)	4 (14.3)	3 (10.7)	7 (12.5)	4 (7.1)
Metabolism and nutrition disorders						
Decreased appetite	3 (10.7)	0	1 (3.6)	0	4 (7.1)	0

Abbreviations: MCD: multicompartment dosimetry; mITT: modified intent-to-treat; n: number of patients with TEAE; SCD: single compartment dosimetry; TEAE: treatment-emergent adverse event

NOTE: Results differ from Garin et al. 2021 due to reanalysis.

Table 10: Summary of all Related Treatment-Emergent SAEs by system organ class and preferred term (mITT population)

	MCD (N = 28)		**SCD** (N = 28)		**Overall** (N = 56)	
MedDRA SOC or Preferred Term	**n (%)**	**nAE**	**n (%)**	**nAE**	**n (%)**	**nAE**
Number of patients with at least one related treatment-emergent SAE	**2 (7.1)**	**3**	**5 (17.9)**	**5**	**7 (12.5)**	**8**
GI disorders (Ascites, GI hemorrhage)	1 (3.6)	1	2 (7.1)	2	3 (5.4)	3
General physical health deterioration	0	0	1 (3.6)	1	1 (1.8)	1
Hepatobiliary disorders Hepatic failure/necrosis/hyperbilirubinemia	2 (7.1)	2	2 (7.1)	2	4 (7.1)	4

Abbreviations: MCD: multicompartment dosimetry; mITT: modified intent-to-treat; n: number of patients with AE; nAE: number of AE occurrences; SCD: single compartment dosimetry; SOC: system organ class; TEAE: treatment-emergent adverse event

NOTE: Results differ from Garin et al. 2021 due to reanalysis.

EVALUATION OF EFFICACY IN THE DOSISPHERE STUDY

The primary endpoint of ORR by investigator at Month 3 according to EASL criteria in the treated population was 71.4% (20/28 patients) and 35.7% (10/28 patients) in the MCD and SCD arms, respectively (P=0.0074). Results were confirmed by centralized evaluation.

Resection after TheraSphere Microspheres treatment

Resection after SIRT was performed in a statistically significantly higher proportion of patients in the MCD arm as compared with the SCD arm: 10/28 (35.7%) for the MCD arm (6/18 PVT patients) vs 1/28 (3.6%) for the SCD arm (0/21 PVT patients) (p=0.0025).

Overall survival (OS) and Progression-free survival (PFS)

Analyses of OS and PFS in the treated population are provided in Table 11. Median OS in the MCD arm was statistically longer versus in the SCD arm.

Table 11: Analyses of OS and PFS According to EASL Criteria in the ITT population (*Garin et al, 2021 & 2024*)

Population	**MCD Arm N=31**	**SCD Arm N=29**	**HR (95% CI) p-value**
Garin E et al, Lancet Gastroenterol Hepatol. 2021 Jan;6(1):17-29. Median Follow-up of 27.2 months (IQR – 33.9–18.7).			
Overall Survival, median, months (95% CI)	26.6 (11.7–NR)	10.7 (6.0–16.8)	0.42 (0.21–0.83) p=0.0096
Subgroup of patients with PVT, months (95% CI)	22.9 (9.1–NR)	9.5 (5.3–17.6)	0.39 (0.17–0.90) p=0.023
Progression, event (%)	17 (54.8%)	17 (58.6%)	
PFS, median, months (95% CI)	6.0 (3.5–11.6)	3.4 (2.9–8.5)	0.71 (0.39–1.30) p=0.26
Garin E et al, J Nucl Med. 2024 Feb 1;65(2):264-269. Median follow-up was 65.8 months (range, 2.1–73.1 months).			
Overall Survival, median, months (95% CI)	24.8 (11–36.5)	10.7 (6–14.9)	0.51 (0.29–0.9) p=0.020
Subgroup of patients with PVT, months (95% CI)	22 (10.3–36.5)	9.4 (5.3–17.6)	0.52 (0.26–0.1) p=0.058

Abbreviations: CI confidence interval; EASL: European Association for the Study of the Liver; HR: Hazard Ratio; ITT: intent-to-treat; MCD: multicompartment dosimetry; NR: not reached; PVT: portal vein thrombosis, PFS: progression free survival; SCD: single compartment dosimetry

Radiation Dosimetry Planning Precision

Y-90 SPECT/CT or Y-90 PET/CT (N=43) imaging was acquired in DOSISPHERE patients for exploratory analysis of differences between planning- and treatment-day records of administered radioactivity (GBq) and HCC index tumor absorbed dose (Gy). Planning day here refers to the day of Tc-99m macroaggregated albumin (MAA) administration. The results of this analysis are shown in Table 12.

Table 12: Radiation Dosimetry Planning Precision

Study patients in whom measured[a] delivery was equal to the planned amount ± 20%:	**Numerator/Denominator = Percentage (%) (95% confidence interval)**	
	MCD Arm	**SCD Arm**
Administered activity (GBq)	22/28[b] = 79 (59,92)	24/28[b] = 86 (67,96)
Tumor absorbed dose (Gy)	5/22[b] = 23 (8,45)	6/21[b] = 29 (11,52)

[a] Measurement based on central review unblinded to investigator-recorded planning information.
[b] Of the 56 (28+28) subjects who received a first Y90 treatment (58 vials), 43 (22+21) received post-Y90 imaging,

including 3 who had multiple investigator-recorded tumor target dosing plans. A subject was counted for the percentages shown if the measured delivery corresponding to each vial and target was equal to the planned activity (GBq) and tumor dose (Gy) ± 20%; missing data was imputed conservatively.

TARGET

TARGET Study: Design, Patient Characteristics and Endpoints

TARGET was a retrospective multinational, single arm study using Simplicit90Y dosimetry software to evaluate multicompartment dosimetry (MCD) in adult patients with HCC who received TheraSphere Microspheres according to local standard of care. MCD was assessed retrospectively. The objective was to explore the relationship between normal tissue absorbed dose (NTAD) and safety outcomes and the relationship between tumor absorbed dose (TAD) and efficacy outcomes. Patients were eligible for inclusion if they had been treated with TheraSphere Microspheres, had unilobar/bilobar disease with up to 10 well-defined HCC tumor(s) per lobe with at least one tumor ≥3 cm ± PVT, had Child-Pugh stage A or B7 and were BCLC A, B or C. Patients were selected in reverse chronological order to minimize selection bias, based on the date of TheraSphere Microspheres treatment, between 01/01/2010 and 12/31/2017.

A total of 209 patients were enrolled at 13 sites in 8 countries. Relevant baseline patient characteristics are summarized in Table 13.

Table 13: TARGET study population baseline characteristics

Baseline Characteristics	**TARGET Population** **N = 209** n (%)
Median age, years (range)	66 (27-87)
BCLC A/B/C	27 (12.9) / 68 (32.5) / 114 (54.5)
Child-Pugh A (5-6)	187 (89.5)
ALBI grade 1/2	80 (38.3) / 123 (58.9)
Portal vein invasion	69 (33.0)
HCC Solitary / Multifocal	 145 (69.4) / 64 (30.6)
Target lesion longest diameter, by mRECIST <5 cm ≥5 to <8 cm ≥8 cm	 51 (24.4) 75 (35.9) 77 (36.8)
Baseline bilirubin <1.0 mg/dL ≥1 mg/dL	 142 (67.9) 67 (32.1)
Baseline AFP (N = 187) ≥200 ng/mL ≥400 ng/mL	 71 (34.0)60 (28.7)

Evaluation of Safety in the TARGET Study

The safety analysis was limited to related adverse events with onset within 90 days. Adverse events occurring after 90 days may not have been detected. Table 14 summarizes the most frequently reported related AEs by severity. No related AEs that occurred within 90 days post-treatment led to death. One patient (0.5%) died due to a related AE of hepatic failure; this death occurred 132 days after the initial TheraSphere Microspheres administration and was due to a later worsening of this event.

Table 14: Related Adverse Events Reported by ≥5% of Patients in TARGET by Severity Grade

Preferred Term	**All Grades N=209 n (%)**	**Grades 3-4 N=209 n (%)**
Total number of patients (N=131) with n=324 of related AEs and SAEs		
Ascites	38 (18.2)	10 (4.8)
Fatigue	34 (16.3)	1 (0.5)
Elevated bilirubin (blood bilirubin increased, hyperbilirubinemia)	29 (13.9)	9 (4.3)
Abdominal pain	26 (12.4)	2 (1.0)
Lymphocyte count decreased	25 (12.0)	16 (7.6)
Asthenia	19 (9.1)	1 (0.5)
Decreased appetite	13 (6.2)	1 (0.5)
Nausea	11 (5.3)	0

A total of 31 related SAEs occurred in 13 patients (6.2%); of these related SAEs, 1 event was Grade 2, 19 events were Grade 3, and 11 were Grade 4. The most frequently reported SAEs by preferred term were ascites (6 events, 5 patients), blood bilirubin increased (3 events, 3 patients), peripheral edema (2 events, 2 patients), and esophageal varices hemorrhage (2 events, 1 patient). Three SAEs were considered life-threatening by the investigator: peritonitis and sepsis experienced by 1 patient and blood albumin decreased experienced by 1 patient.

No association was identified between perfused NTAD and the occurrence of hyperbilirubinemia of Grade 3 or higher (bilirubin >3 times ULN per CTCAE V4.02) in the absence of disease progression (primary endpoint) or between perfused NTAD or to whole liver NTAD and the occurrence of a dose related AE of interest (hyperbilirubinemia, ascites, pain, fatigue, nausea, and post-embolization syndrome).

Evaluation of Efficacy in the TARGET Study

The main efficacy results from the TARGET study are shown in Tables 15.

Table 15: Objective Response Rate

	Population N=209 % (n)	**95% CI[a]**
ORR, All lesions, mRECIST	61.7 (129)	55.0, 68.0
ORR, Target lesion, mRECIST	70.8 (148)	64.3, 76.6

[a] Based on Wilson Methodology

N: total number of patients included in analysis; CI: confidence interval

POST APPROVAL STUDY: TC-99M MAA RELATED IRRADIATION

This post-market, prospective, single-arm, open-label, observational study was conducted to determine the radiation-absorbed dose to the whole body and to potential irradiated non-liver critical organs following intrahepatic Tc-99m macroaggregated albumin (MAA) administration in patients with planned TheraSphere administration. One US clinical study site enrolled six patients undergoing evaluation for TheraSphere administration; one patient withdrew consent, and 5 patients completed the study. All patients who completed the study were imaged at three timepoints: by SPECT-CT imaging immediately following Tc-99m MAA

procedure, by SPECT imaging at 4 (± 2) hours after Tc-99m MAA procedure and by SPECT imaging between 18 and 24 hours after Tc-99m MAA procedure. Subsequent follow-up visits were per standard of care.

The study endpoints were mean absorbed dose and delivered activity for whole body and non-liver critical organs (including whole body effective dose). Critical organs evaluated included liver, lungs, salivary glands, thyroid gland, kidneys, spleen, heart wall, and mucosa/wall of the stomach, gallbladder, small intestine, colon and urinary bladder. Results showed the majority of Tc-99m MAA mean delivered activity was localized to the liver rather than to non-liver critical organs. Results are summarized in Table 16 and Table 17. There were no reports of adverse events or serious adverse events related to the Tc-99m MAA administration procedure or subsequent imaging. These results are in line with expectation for Tc-99m MAA radiation exposure and demonstrate that it is safe for use in patients with a planned TheraSphere administration given the potential benefits of this device for treatment of their cancer.

Table 16: Mean Delivered Activity from SPECT, and Mean Absorbed Dose for Whole Body, Liver, and Non-Liver Critical Organs

	Delivered Activity from SPECT (MBq)			**Absorbed Dose (mGy/MBq)**	**Whole Body Effective Dose (mSv/MBq)**
	Immediately following Tc-99m MAA procedure	**4 (± 2) hours post procedure**	**≥ 18 to <24 hours post procedure**		
Whole Body Mean (SD)	67.32 (15.96)	27.98 (9.45)	1.69 (1.52)	0.26 (0.04)	0.009 (0.0013)
Liver Mean (SD)	60.29 (14.77)	19.34 (5.29)	1.03 (0.80)	0.07 (0.02)	N/A
Non-Liver Critical Organs Mean (SD)	6.99 (3.89)	8.64 (4.75)	0.66 (0.63)	0.18 (0.04)	N/A

SD: standard deviation
Note: Whole body activity measurements are the sum of measurable critical organ activities. Whole body absorbed dose coefficients are the sum of all critical organ absorbed dose coefficients.

Table 17: Estimated Absorbed Dose Measurements from the Tc-99m MAA Irradiation Study

Organ	**Absorbed Dose per Unit Activity (mGy/MBq)**		**Mean Total Absorbed Dose[a] (mGy)**	
	Mean	SD	Mean	SD
Adrenals	0.019	0.005	1.46	0.27
Brain	0.00005	0.00001	0.003	0.002
Breast	0.004	0.001	0.28	0.05
Colon wall	0.005	0.001	0.37	0.06
Endosteum (bone surface)	0.002	0.0003	0.12	0.02
ET region	0.0003	0.0001	0.02	0.01
Eye lenses	0.0001	0.00001	0.007	0.002
Gallbladder wall	0.032	0.007	2.39	0.41
Heart wall	0.008	0.002	0.57	0.09
Kidneys	0.029	0.010	2.19	0.59
Liver	0.074	0.019	5.70	1.64

Lung	0.008	0.001	0.59	0.09
Lymphatic nodes	0.004	0.001	0.31	0.05
Muscle	0.001	0.0003	0.09	0.02
Oesophagus	0.007	0.001	0.51	0.07
Oral mucosa	0.0002	0.00004	0.02	0.00
Pancreas	0.017	0.004	1.25	0.22
Prostate	0.001	0.001	0.08	0.04
Red (active) bone marrow	0.003	0.001	0.25	0.04
Salivary glands	0.0002	0.00004	0.018	0.003
Skin	0.001	0.0002	0.06	0.01
Small intestine wall	0.004	0.001	0.29	0.05
Spleen	0.008	0.002	0.57	0.12
Stomach wall	0.011	0.003	0.83	0.14
Testes	0.0001	0.00004	0.006	0.003
Thymus	0.002	0.0004	0.18	0.03
Thyroid	0.009	0.012	0.69	0.93
Urinary bladder wall	0.006	0.008	0.49	0.68
[a] Mean administered activity 76.5±7.1 MBq				

HOW SUPPLIED

Device Details

The TheraSphere Microspheres dose vials are steam sterilized and are available in 0.5 GBq increments between 3 GBq - 20 GBq (13.5 mCi increments between 81 mCi - 540 mCi). All dose sizes have a manufacturing tolerance of ±10 % of nominal activity. The glass microspheres are 15 µm - 35 µm in size, with each milligram dose containing between 22,000 and 73,000 microspheres, supplied in 0.6 mL pyrogen-free water in a V-bottom vial enclosed in an acrylic shield.

The other components of the TheraSphere Y-90 Glass Microsphere System required for administration include:

- a sterile, single-use Administration Set and
- a non-sterile, re-usable Administration Accessory Kit.

Do not use if package is damaged or unintentionally opened before use.

Do not use if labeling is incomplete or illegible.

Handling and Storage

Handling and Radiation Safety

- Consult and follow all applicable regulatory agency requirements for safe handling and storage of radioactive materials. TheraSphere Microspheres contain Y-90, a high-energy beta emitter.
- The TheraSphere Microspheres dose vial is supplied in an acrylic shield to fully attenuate beta particles and within a lead pot to further limit radiation exposure to secondary bremsstrahlung (x-ray) radiation. The TheraSphere Microspheres dose vial should always be stored in a shielded location away from personnel.
- Always wear disposable gloves when handling the dose vial. Routinely check for radioactive contamination after handling.
- The procedure is normally performed in an angiography suite where personnel wear shielding aprons with thyroid protection. No additional personal safety equipment is needed for use of TheraSphere Microspheres. The primary risk of radiation exposure for this procedure is from fluoroscopy during

catheter placement. Personnel exposure should be monitored according to the local procedure.

- After the treatment, any spills or leaks must be cleaned up immediately. The treatment area and all personnel handling radioactive materials should be monitored for contamination.
- Radioactive waste must be contained and stored for waste disposal according to hospital procedures for radioactive materials.

Radiation Safety Warnings

- Keep the TheraSphere Microspheres dose vial upright and stored in its lead pot before and during patient treatment, except as required for radiation measurement. Failure to do so could cause radiation exposure or damage to the product.
- Do not open the dose vial acrylic shield prior to patient treatment.
- Beta radiation from the tubing and exposed microcatheter is highest during microsphere transfer. Stand behind shielding and/or maintain distance.
- Post-treatment, waste materials require caution to prevent contamination and beta shielding due to residual glass microspheres. [See ***Cleanup of Administration System***]
- As in the use of any radioactive material, ensure minimum radiation exposure to the patient unrelated to the therapeutic objective, and to minimize radiation exposure to workers and others in contact with the patient.

Lead handling

The TheraSphere Microspheres dose vial is supplied in a lead pot. Safe handling and disposal for this material should be used to avoid lead contact. [See ***Cleanup of Administration System***]

Storage

This product has no special storage requirements beyond those required for radioactive material.

DOSING AND ADMINISTRATION INSTRUCTIONS

Recommended Dose (Radiation Segmentectomy/Partition Method)

When planning for a radiation segmentectomy, the recommended radiation absorbed dose to the target perfused volume is ≥ 400 Gy. A radiation segmentectomy can be defined and should be considered when adequate tumor target margins can be achieved by a site of perfusion at the segmental or sub-segmental level. Recommended normal lung tissue constraints are 30 Gy per treatment and 50 Gy cumulatively.

When planning to perfuse multiple liver segments separable into a perfused tumor partition and a perfused normal liver partition, the recommended radiation absorbed dose to the target tumor partition is ≥205 Gy and, if possible, ≥250 Gy or even ≥300 Gy. Recommended normal tissue constraints are 120 Gy to the perfused normal liver if the hepatic reserve is 30%. Higher normal tissue absorbed dose is acceptable in the case of segmental treatment and with hepatic reserve >30%. Recommended normal lung tissue constraints are 30 Gy per treatment and 50 Gy cumulatively.

The recommended prescribed activity is the maximum amount calculated to meet the recommended target range while not exceeding the referenced normal tissue constraint.

Formulas for calculating prescribed activity based on recommended dosing are provided below.

Technique for Lung Shunt Evaluation
To assess arterial perfusion of the liver and the fraction of radiopharmaceutical tracer that will pass through the liver and lodge in the lungs:

- Inject 75 MBq to 150 MBq (2 mCi to 4 mCi) of ^{99m}Tc MAA via a catheter with the tip placed within 5 mm of the anatomical position from which the TheraSphere Microspheres will be administered.
- Use a large FOV gamma camera, and obtain images of the thorax and abdomen in one acquisition.
- Draw ROI around the whole liver and the whole lung and get the total counts for the lung and the

liver.

- Calculate the lung shunt fraction (F) using the following formula:

$$F = \left(\frac{Lung\ Counts}{Liver\ Counts + Lung\ Counts}\right)$$

Activity that may potentially reach the lung:

$$\boldsymbol{A_{lung}} = \boldsymbol{A_{total}} \times \boldsymbol{F}$$

Where:
A_{lung} = lung activity [GBq]
A_{total} = total prescribed activity [GBq]
F = lung shunt fraction

Activity Calculation

The dosimetry methodology is based on the application of the MIRD schema, the partitioning of administered activity between tumor and non-tumor compartments within the perfused volume, and the assumption that the activity distribution is homogeneous within each compartment. Partition-based dosimetry distinguishes between tissue compartments intended to receive therapeutic absorbed dose (e.g., tumor target) and tissue compartments intended to be spared (e.g., normal tissue). This approach can be implemented using patient specific defined volumes of interest within the perfused volume and compartments. When the perfused volume is modeled as tumor target and normal tissue compartments, this framework is consistent with tumor–normal ratio–based partition formulations [see ***Appendix***].

A generalized formula for calculation of mean absorbed dose to a VOI within the perfused volume(s), D_{VOI}, requires:

1. The activity (GBq) in the perfused volume (PV), A_{PV}, calculated from the activity in the vial(s) at time of treatment (A), accounting for residual fraction (R) and lung shunt fraction (F) through: $A_{PV} = A \times (1 - R) \times (1 - F)$
2. An estimate of the tissue mass (kg) in the VOI, M_{VOI}
   - The tissue mass is related to the density (ρ = 1.03 x 10^{-3} kg/mL = 1.03 x 10^{-3} kg/cm^3) and volume (V_{VOI}) of the VOI in cm^3 through: $M_{VOI} = \rho \times V_{VOI}$
3. The counts in the VOI, C_{VOI}
4. The total counts in the perfused volume(s) intended for treatment, C_{PV}
5. The energy deposited in tissue over time per unit activity administered (50 Gy·kg/GBq = 50 J/GBq).
6. A patient relative calibration factor, CF (GBq/Counts), relating administered activity to counts in the perfused volume(s), can be calculated using the following formula:

$$CF = \frac{A_{PV}}{C_{PV}}$$

The VOI absorbed dose, $D_{VOI,}$ is then:

$$D_{VOI} = \frac{50 \times C_{VOI}}{M_{VOI}} \times \frac{A_{PV}}{C_{PV}} = \frac{50 \times C_{VOI}}{M_{VOI}} \times CF$$

The activity required to deliver a target absorbed dose to a VOI, $D_{VOI,target,}$ within the perfused volume(s) can be calculated by rearranging the equation:

$$A = \frac{D_{VOI,target} \times M_{VOI} \times C_{PV}}{50 \times (1 - R) \times (1 - F) \times C_{VOI}}$$

The required activity is adjusted, as needed, to meet VOI absorbed dose objectives (e.g. TAD or NTAD).

<u>Radiation Segmentectomy</u>

For radiation segmentectomy, the VOI is the entire perfused volume, therefore $C_{VOI} = C_{PV}$ and $M_{VOI} = M_{PV}$. The equation to determine D_{PV} then reduces to:

$$D_{PV} = \frac{50 \times C_{PV}}{M_{PV}} \times \frac{A_{PV}}{C_{PV}} = \frac{50 \times A_{PV}}{M_{PV}}$$

Rearranging, the activity required to deliver a target absorbed dose to the perfused volume, $D_{PV,target}$ is then:

$$A = \frac{D_{PV,target} \times M_{PV}}{50 \times (1 - \mathrm{R})(1 - \mathrm{F})}$$

The required activity is adjusted, as needed, to meet perfused volume absorbed dose objectives.

Lung Dose

To determine the lung dose, D_{Lung}, given that a fraction of activity may shunt from the liver to the lung:

$$D_{Lung} = \frac{50 \times A(1 - \mathrm{R}) \times \mathrm{F}}{M_{Lung}}$$

Where M_{Lung} may be measured from patient-specific CT imaging or assumed to be 1kg.

TheraSphere Microspheres treatment should be personalized. Prior to treatment, the user should define the treatment objective and consider:

- the administration technique: selective (sub-segmental/segmental) or nonselective (lobar),
- the number of vials (multiple administrations) and/or additional planned retreatment(s),
- the dosimetry method: radiation segmentectomy or MCD.

Pre-Treatment Process (Completed Prior to Dose Vial Administration)

Prior to the administration of TheraSphere Microspheres, treatment planning must be performed to determine patient eligibility for TheraSphere Microspheres administration and for determining the appropriate catheter placement for the TheraSphere Microspheres administration. Use of a 3D imaging tool is recommended, including cone beam computed tomography (CBCT) or computed tomography scanner (CT scan) to visualize the perfused volume of liver.

1. Tc-99m MAA Administration

Tc-99m MAA is used as a proxy for TheraSphere Microspheres and an activity of Tc-99m from 75 MBq to 150 MBq (2 mCi to 4 mCi) should be infused during the pre-treatment angiography into the selected hepatic artery(ies). The catheter tip position for Tc-99m MAA and planned TheraSphere Microspheres infusion should be the same (i.e., within 5 mm) to ensure accurate predictability of pretreatment MCD. For selective infusions the catheter tip position should be determined by tumor location and patient arterial anatomy.

2. Tc-99m MAA Imaging

Tc-99m MAA estimation of TheraSphere Microspheres TAD and NTAD:

- Tc-99m MAA injected into the hepatic arteries will differentially distribute in the tumor and normal tissue within the perfused liver volume based on blood flow. Pretreatment Tc-99m MAA distribution within tumor and normal tissue VOI can be used to estimate the TheraSphere Microspheres TAD and NTAD. SPECT/CT is recommended to calculate the Tc-99m MAA estimated TAD and NTAD.

Evaluation of PVT targeting

- Enhanced uptake of Tc-99m MAA within PVT relative to normal liver tissue within the perfused liver volume is defined as PVT targeting. In the absence of PVT targeting, but with sufficient TAD, additional treatment options should be considered, i.e., systemic treatment, to treat the PVT.

Note: Sources of uncertainty associated with the derivations of recommended TAD and NTAD include quality of the imaging and registration, reader contouring variability, interval between administration and imaging following Tc-99m MAA preparation due to compound stability, vessel spasm or occlusion (particularly due to Tc-99m MAA), differences in the size, shape and number of Tc-99m MAA particles versus TheraSphere Microspheres, different catheter placement and/or speed of infusion for Tc-99m MAA and TheraSphere Microspheres particularly near a bifurcation, variation associated with the mode of segmentation (anatomic versus count threshold), and for tumors <2 cm (not recommended for pretreatment MCD).

Use of Dosimetry Software and Recommended Doses

The use of commercial dosimetry software devices can be used to perform pretreatment dosimetry planning and post-treatment dosimetry confirmation. Dosimetry calculations for user defined VOIs are performed based on the Medical Internal Radiation Dose (MIRD) schema, using the local deposition method.

Selection of Dose Vial to Order

Use the following formula to determine the appropriate dose vial size to order, that will yield the Activity Required on the date and time of treatment:

Dose Vial Size to Order (GBq) = $\boldsymbol{Activity\ Required\ (GBq) \times 0.9892^{[-1 \times decay\ time(h)]}}$

Where Activity Required comes from the calculation above, and decay time (h) is the number of hours from the date and time of calibration (from the manufacturer) to the date and time of treatment in the local time zone. Calibration date and time is always referenced to Sunday at noon North American Eastern Time zone. The dose vial expiry date is printed on the dose vial label.

The dose vial size to order should be rounded to the nearest 0.5 GBq increment between 3 GBq and 20 GBq (13.5 mCi increment between 81 mCi and 540 mCi); alternatively, a combination of dose vial sizes may be ordered. The dose vial size may be calculated manually based on the formula above or using commercially available dosimetry tools. TheraSphere Treatment Window Illustrator (TWI) assists the user with dose vial selection. Simplicit90Y™ software also includes an integrated dose vial selector feature that can be used to assist the user with dose vial selection. These tools calculate the TheraSphere Microspheres dose vial size options, based on user-specified information on the desired tissue absorbed dose (Gy), treatment date and time, lung shunt fraction and anticipated residual waste. The TWI output is used to place the dose vial order manually.

Dose Vial Activity Confirmation

After receipt of the TheraSphere Microspheres dose vial, confirm it is the correct activity for the patient treatment. Dose calibrator settings for the TheraSphere Microspheres dose vial geometry are determined by cross-reference to a National Institute of Standards and Technology (NIST) traceable measurement, based on the as-manufactured activity provided by the manufacturer.

In addition, measure and record the radiation field from the TheraSphere Microspheres dose vial (in acrylic shield, removed from lead pot) at a fixed distance (template provided) prior to treatment.

OPERATIONAL INSTRUCTIONS FOR THERASPHERE MICROSPHERES ADMINISTRATION

The entire contents of the TheraSphere Microspheres dose vial are administered to the patient. The administration instructions must be followed to optimize delivery of the prescribed dose. For the administration of multiple dose vials see ***Administration of Multiple TheraSphere Microspheres Dose Vials***.

Additional Items for Safe Use

Materials required for the administration of TheraSphere Microspheres include:

- Sterile saline solution (e.g. 0.9 % saline)
- An appropriately positioned microcatheter [see ***Microcatheter Selection and Positioning***]
- A prepared cart with the TheraSphere Microspheres device [see ***Preparation for TheraSphere Microspheres Administration***]
- Components used for an arterial catheterization procedure will also be required guide catheter/sheath,

guidewire, introducer)

Microcatheter Selection and Positioning

Apply the following when selecting a microcatheter for the administration of TheraSphere Microspheres:

- A microcatheter with an internal diameter of ≥ 0.5 mm (0.020 inch) should be used to deliver TheraSphere Microspheres. Using a smaller microcatheter diameter will cause restricted flow in the administration system, which may cause microspheres to be retained in the TheraSphere Administration Set and in the microcatheter. This could result in an under-dose.
- The microcatheter must not occlude the vessel in which it is placed. The administration of TheraSphere Microspheres is dependent on blood flow through the hepatic vasculature distal to the microcatheter tip to carry the microspheres into the perfused tissue.
- Microcatheter lengths of 120 cm to 155 cm (typically for femoral artery access) and > 130 cm (typically for radial artery or arm access) may be suitable. A microcatheter that is too short may be difficult to connect to the Administration Set outlet.
- **Do not use extension tubing** between the TheraSphere Administration Set and the microcatheter. The use of extension tubing will cause significant residual microspheres that will result in an under-dose.
- The use of fittings (e.g., stopcocks) between the TheraSphere Administration Set and the microcatheter is expected to cause residual microspheres that could result in an under-dose. Added fittings may also introduce a risk of misdirected microspheres.
- For infusion the catheter tip position should be determined by treatment goal, tumor(s) location and patient arterial anatomy.

Preparation for TheraSphere Microspheres Administration

- Confirm patient identity and prescription for TheraSphere Microspheres against measured dose and treatment location (e.g., signed Written Directive)
- Prepare the treatment room with appropriate equipment (e.g., radiation detector, spill kit) and signage. Apply a floor cover under the treatment area in the angiography suite.
- Prepare a moveable cart with the following items:
  - Small sterile towels/drapes
  - Saline bag or bottle – one per dose vial, minimum 200 mL size
  - Hemostat/Kelly forceps or similar
  - Adhesive strips
  - Alcohol disinfectant
  - Scissors
  - TheraSphere Administration Set(s) – one set per dose vial. Ensure the packaging for the TheraSphere Administration Set is intact before use. If package integrity has been breached prior to use, discard the item and obtain a new one. Do not use expired TheraSphere Administration Sets.
  - TheraSphere Administration Accessory Kit
  - Electronic dosimeter (RAD 60 or equivalent) clipped onto Administration Accessory Kit and set to display instantaneous dose rate (µSv/h or mR/h)
  - Waste container with beta shield (e.g., 2 L wide-mouth plastic jar with screw lid, with acrylic beta shield)
  - TheraSphere Microspheres dose vial(s), in lead pot

Administration Set Priming

- Open the Administration Set packaging
- Connect the fluid spike into the saline bag and hang saline on the bag hook
- Connect the vented spike to the empty overflow vial
- Remove the cap from the needle injector assembly. The yellow tabs should be fully retracted to lock needles in enclosed position. Place the needle injector assembly on a sterile surface.

  Precaution: Two needles are located inside injector assembly. When removing the cap from the needle injector assembly, follow standard sharps procedure.

- Prime the Administration Set with saline until bubbles are removed and saline flows continuously out of both needle injector assembly holes

- Fill the syringe when priming is complete

Dose Vial Preparation and Assembly with Administration Set

- Tilt the TheraSphere Microspheres dose vial (in its lead pot) back and forth to 90° and tap it sharply on a hard surface
- Put the dose vial (in its lead pot) into the acrylic box and remove the lead pot lid
- Remove the dose vial security seal and dose vial access plug from the acrylic shield and put into waste container. The dose vial access plug can be removed using an adhesive strip as required.
- Disinfect the dose vial septum with alcohol
- Place the overflow vial and tubing 'A' into the overflow vial holder and gripper clip on the acrylic box
- Connect the Administration Set needle injector assembly to the dose vial by pressing on the green cap
- Place tubing through slots 'B' and 'D', and slide fitting near label 'C' into the holder at 'C'
- Close the blue pinch clamp at tubing label 'C'

Final Assembly (Immediately Before Administration)

- Close the white pinch clamp on tubing near label 'E'
- Push down on both yellow tabs, sliding past the second detent, to fully insert needles into dose vial
- Put the lid on the acrylic box
- Lower the bed height and move the cart beside the bed
- Place sterile towel/drape under the steel arm 'E', and across the gap from the Administration Accessory Kit to the patient
- Interventional Radiologist (IR) to verify microcatheter position and flush it with saline to ensure flow
- Disconnect the outlet luer 'E' from the holder at 'C' and firmly connect to the microcatheter
- Place the microcatheter connection in the holder on the extension arm (fully extended) with the microcatheter hanging vertically below
- Ensure the tubing and microcatheter are free of kinks

TheraSphere Microspheres Administration

Warning: Beta radiation from the tubing and exposed microcatheter is highest during microsphere transfer. Stand behind shielding and/or maintain distance.

- Open the white pinch clamp from tubing at 'E' and relieve the indent
- Record the electronic dosimeter initial reading and starting time of the administration
- Using steady pressure, flush the syringe at ≥ 20 mL/min to administer TheraSphere Microspheres
- Re-fill the syringe and repeat flushing; a minimum of 3 flushes (60 mL total) is recommended
- Record the electronic dosimeter final reading (value indicating contents of dose vial)

NOTE: If the syringe flow is < 20 mL per minute this may cause increased residual microspheres.

NOTE: Dripping into the overflow vial is normal operation; most or all flow going into overflow vial indicates an obstruction in the flow path or microcatheter.

DISSASEMBLY AND RADIATION WASTE

- At completion of treatment, cut the tubing at the indicated position and open the acrylic box
- Close the white pinch clamp on the outlet tube at 'E'
- IR to remove the microcatheter from the patient, using care to control the tip. Do not disconnect the microcatheter from the outlet tubing.
- Place all radioactive contaminated waste into the waste container (in its beta shield) and close waste container. Reserve for measurements to determine percent delivery and for disposal. [See ***Calculation of Activity Delivered to Patient***]
- Check the hands of all operators for microsphere contamination, as well as equipment and the treatment area. Contain and dispose of items as appropriate.

- Radiation from the patient may be measured after treatment.

To minimize the potential of a high radiation hand dose, use a hemostat, forceps, or towels/gauze when handling parts of the Administration Set after infusion.

Administration of Multiple TheraSphere Microspheres Dose Vials

- When prescribed in the treatment plan, more than one dose vial may be administered to the same patient during the same treatment session.
- After removing the contaminated items and waste container, and after confirming there is no radioactive contamination on the operators hands, torso, or equipment, the IR may put on new sterile gloves to place a new microcatheter.
- Proceed to administer the next dose vial following these operational instructions.

Cleanup of Administration System

- Use a radiation detector to check for contamination on the cart, lead pot, equipment, and the areas under the catheter connection and cart.

Note: Radiation from fluoroscopy, the patient, and the waste container will affect the ability to detect and measure contamination.

- Decontaminate radioactive components as appropriate.
- As required, the TheraSphere Microspheres Administration Accessory Kit may be cleaned with a clean, soft cloth, using alcohol or chlorine cleaning agents. The use of solvents, abrasive cleaners, ammonia, or heat/steam may damage the acrylic parts and should be avoided. Removable stainless steel parts are compatible with cleaning by chemical/heat/steam process.
- Replace the top and side shields on the acrylic box. Retract the extension arm and remove the bag hook.
- Turn off the dosimeter.
- Store the Administration Accessory Kit.

Disposal of Non-Radioactive Items

To minimize the risk of infection or microbial hazards after use, dispose of non-radioactive items and packaging as follows:
After use, non-radioactive items and packaging may contain biohazardous substances. Any items and packaging that came into contact with biohazardous substances should be treated and disposed of as biohazardous waste or be treated and disposed of in accordance with any applicable hospital, administrative, and/or local government regulations. Use of a biohazardous container with biological hazard symbol is recommended. Untreated biohazardous waste should not be disposed of in the municipal waste system.

Calculation of Activity Delivered to Patient

The percentage of activity that was delivered to the patient is calculated using the following equation, based on radiation measurements of the dose vial (in acrylic shield, removed from lead pot) at a fixed distance (template provided) prior to treatment, compared to measurements of the waste materials after the treatment.
After treatment, the 4 sides of the waste container inside a beta shield are measured at the same fixed distance using the same radiation meter, and the four measurements are averaged.

$$\boldsymbol{Percentage\ of\ Dose\ Delivered}(\%) = [\mathbf{1} - \frac{\boldsymbol{Average\ of\ Waste\ Measurement\ after\ Administration}}{\boldsymbol{Dose\ Vial\ Measurement\ before\ Administration}}]\boldsymbol{x100}$$

where the Dose Vial Measurement is adjusted for the radioactive decay of Y-90 until the time that the Waste Measurement is made (i.e., 1% decay per hour).

POST-TREATMENT IMAGING AND DOSIMETRY

Post treatment imaging may be performed to evaluate Y-90 glass microsphere distribution and resulting absorbed dose in the tumor and non-tumor tissue as a quality control measure and to guide subsequent patient care. It also may be used to confirm the absence of non-target microspheres. Post-treatment images may be analyzed in comparison to pretreatment Tc-99m MAA images.

Post-treatment imaging of Y-90 may be performed using gamma cameras or SPECT/CT to detect Bremsstrahlung radiation, or by Positron Emission Tomography (PET)/CT to detect photon pairs from Y-90 positron emissions. For optimal imaging signal, imaging should be performed within 24 hours of TheraSphere Microspheres administration.

Post-treatment dosimetry is performed as described above for pretreatment dosimetry. Treatment day administered activity (accounting for residual fraction and expected lung shunt fraction estimated from Tc-99m MAA imaging) is used to determine mean absorbed dose to the defined VOIs.

The TheraSphere Microspheres Written Directive tool may be used to aid in calculating the percentage of dose delivered and actual radiation dose delivered, documenting the administration as required by regulation. This tool is available by contacting your local Boston Scientific representative.

RELEASE AND POST-PROCEDURE

Assess patient for hematoma and/or other signs of bleeding at the puncture site. Any serious incident that occurs in relation to this device should be reported to the manufacturer and relevant local regulatory authority.

Precaution: Use universal precautions for body fluid contact. Trace Y-90 may be detectable in blood and urine; handle with gloves and dispose as normal body fluids. The radiation field is expected to be less than 10 µSv/h (1 mrem/h) at 1 m (3 ft) from the patient's abdomen. Supplemental shielding and segregation of the patient are not required to maintain exposure to others below regulated limits.

Precaution: The patient should follow good hygiene (e.g. proper hand washing). Caregivers, family, and others do not require restrictions on patient contact, however they can minimize their radiation exposure by avoiding prolonged time (>12 hours per day) within 0.3 m (1 ft) of the patient's abdomen for the first week post therapy. Patients should be advised that radiation emitted from the patient may be detectable at security screening.

Precaution: Advise the patient that if the patient requires hospitalization, surgery, medical assessment or treatment regarding any part of their thorax or abdomen within first 2 weeks of treatment, the patient should inform the hospital and treating physician of the Y-90 TheraSphere Microspheres implant so that proper radiation precautions can be taken.

See also ***Precautions and Patient Counseling Section***.

Implantable Device Patient Information

Advise the patient that additional information may be available to them on the Boston Scientific website (www.bostonscientific.com/patientlabeling).

Implantable Card Instructions

Record the institution name, patient details, and implant date. Add a peel-off label from product packaging. Provide to patient.

PATIENT COUNSELING SECTION

The physician should consider the following points while counseling patients on the use of TheraSphere Microspheres in association with the interventional procedure:

- Discuss patient allergies in particular the risk for patient who may be allergic to contrast.
- Discuss the risk and benefits of including review of potential adverse events listed in this document, both for TheraSphere Microspheres and for other alternative treatments.
- Discuss post procedure instructions, including any lifestyle changes, medications, and homecare or rehabilitation recommendations.
- Discuss post-procedure care related to radiation, specifically the patient should follow good hygiene (e.g., proper hand washing). Caregivers, family, and others do not require restrictions on patient contact; however, they can minimize their radiation exposure by avoiding prolonged time (> 12 hours per day)

within 0.3 m (1 ft) of the patient's abdomen for the first week post therapy.

- Advise the patient that if the patient requires hospitalization, surgery, medical assessment, or treatment regarding any part of their thorax or abdomen within first 2 weeks of treatment, the patient should inform the hospital and treating physician of the Y-90 TheraSphere Microspheres implant so that proper radiation precautions can be taken.
- Discuss with the patient that the glass microspheres remain permanently implanted in the liver tissue and should be disclosed if cremation is considered.
- Advise the patient that radiation emitted from the patient may be detectable at security screening (e.g., international travel).

Expected Lifetime

The glass microspheres are implantable and materials of the device are nonbiodegradable and are intended to last for the lifetime of the patient.

REFERENCES

Healthcare professionals should consult recent literature regarding TheraSphere Microspheres administration.

WARRANTY

For device warranty information, visit www.bostonscientific.com/warranty.

SYMBOL DEFINITIONS

Commonly used medical device symbols that appear on the labeling are defined at www.bostonscientific.com/SymbolsGlossary.

Additional symbols are defined at the end of this document.

APPENDIX

In the prospectively tested two-compartment (also called two-partition or multi-compartment) dosimetry method, formalisms expressed in terms of VOI or compartment/partition ratios are conceptually identical.

Noting that the identity between a compartment/partition and a VOI need not be 1-to-1, for any perfused volume (PV) modeled as two compartments/partitions, the counts (C) in the perfused volume can be defined as:

$$C_{PV} = C_1 + C_2 \quad (1)$$

The following example illustrates the situation in which the conceptual compartments 1 and 2 correspond directly to VOI-defined tumor target and normal regions which comprise the entire PV. The tumor-to-normal-ratio (TNR) is calculated based on the counts and the mass (M) of the tumor target and normal compartments:

$$TNR = \frac{\frac{C_{Target}}{M_{Target}}}{\frac{C_{Normal}}{M_{Normal}}} \quad (2)$$

The activity required to deliver a specified absorbed dose to the tumor target VOI is:

$$A = \frac{D_{Target} \times M_{Target} \times C_{PV}}{50 \times (1-R) \times (1-F) \times C_{Target}} \quad (3)$$

Considering (1), (3) may be expressed as:

$$A = \frac{D_{Target} \times M_{Target} \times (C_{Target} + C_{Normal})}{50 \times (1-R) \times (1-F) \times C_{Target}} \quad (4)$$

Rearranging (2):

$$\frac{M_{Normal}}{TNR} = \frac{M_{Target} \times C_{Normal}}{C_{Target}}$$

$$\rightarrow \quad M_{Target} + \frac{M_{Normal}}{TNR} = \frac{M_{Target} \times (C_{Target} + C_{Normal})}{C_{Target}}$$

Substituting this into (4) results in the TNR partition model form:

$$A = \frac{D_{Target} \times M_{Target} \times (C_{Target} + C_{Normal})}{50 \times (1-R) \times (1-F) \times C_{Target}} = \frac{D_{Target} \times (M_{Target} + \frac{M_{Normal}}{TNR})}{50 \times (1-R) \times (1-F)}$$


Activity


Calibration


Contents

MR Safe


Caution Radioactive Material

Recommended Microcatheter

Vial Number

Manufactured for:
Boston Scientific Corporation
300 Boston Scientific Way
Marlborough, MA 01752 USA
USA Customer Service +1-888-272-1001

www.bostonscientific.com

YYYY-MM

51187463-01