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℞ Only

SIR-Spheres® Y-90 resin microspheres

(Yttrium-90 microspheres)

1 Description

SIR-Spheres Y-90 resin microspheres consist of biocompatible microspheres containing yttrium-90 with a size between 20 and 60 microns in diameter. Yttrium-90 is a high-energy pure beta-emitting isotope with no primary gamma emission. The maximum energy of the beta particles is 2.27 MeV with a mean of 0.93 MeV. The maximum range of emissions in tissue is 11 mm with a mean depth of 2.5 mm. The half-life is 64.1 hours. In therapeutic use, requiring the isotope to decay to infinity, 94% of the radiation is delivered in 11 days. The number of particles provided in each SIR-Y001 5mL vial for implantation is 40-80 million microspheres and the number of particles provided in each SIR-Y002 3mL vial for implantation is 24-48 million microspheres. SIR-Spheres Y-90 resin microspheres are a permanent implant.

SIR-Spheres Y-90 resin microspheres are implanted into a hepatic tumor by injection into either the common hepatic artery or the right or left hepatic artery or more selectively using a catheter or chemotherapy catheter port. The SIR-Spheres Y-90 resin microspheres distribute non-uniformly in the liver, primarily due to the unique physiological characteristics of the hepatic arterial flow, the tumor to normal liver ratio of the tissue vascularity, and the size of the tumor. The tumor usually gets higher density per unit distribution of SIR-Spheres Y-90 resin microspheres than the normal liver. The density of SIR-Spheres Y-90 resin microspheres in the tumor can be as high as 5 to 6 times of the normal liver tissue. Once SIR-Spheres Y-90 resin microspheres are implanted into the liver, they are not metabolized or excreted, and they stay permanently in the liver. Each device is for single patient use.

2 Indications for Use

SIR-Spheres Y-90 resin microspheres are indicated for the local tumor control of unresectable hepatocellular carcinoma (HCC) in patients with no macrovascular invasion, Child Pugh-A cirrhosis, well-compensated liver function, and good performance status. They are also indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

3 Contraindications

3.1 Contraindications for All Patients

SIR-Spheres Y-90 resin microspheres are contraindicated in any patient who has:

- portal vein thrombosis
- ascites or clinical liver failure
- markedly abnormal synthetic and excretory liver function tests (LFTs), such as total bilirubin > 2.0 mg/dL or albumin < 3.0 g/dL
- > 20% lung shunting of the hepatic artery blood flow, or > 30 Gy radiation absorbed dose to the lungs for a single treatment, or > 50 Gy cumulative radiation absorbed dose to the lungs if the patient is re-treated, as estimated by the ^{99m}Tc MAA scan
- pre assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of microspheres to the stomach, pancreas or bowel
- had previous external beam radiation therapy to the liver

3.2 Contraindications for Patients with mCRC

[*See Contraindications (3.1)*]

- disseminated extra-hepatic malignant disease
- been treated with capecitabine within the two previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres Y-90 resin microspheres

3.3 Contraindications for Patients with HCC

[*See Contraindications (3.1)*]

- comorbidities or poor overall health (e.g., ECOG performance status rating> 2) which may make the patient a poor candidate for locoregional radiation treatment
- disseminated extra-hepatic malignant disease

4 Warnings

4.1 Non-Target Delivery of SIR-Spheres Y-90 Resin Microspheres

Inadvertent delivery of SIR-Spheres Y-90 resin microspheres to extra-hepatic structures such as the esophagus, stomach, duodenum, gallbladder or pancreas may result in radiation injury to these structures. Meticulous angiographic technique must be employed to prevent the non-target delivery of SIR-Spheres Y-90 resin microspheres to any extra-hepatic structures.

4.2 Radioembolization Induced Liver Disease (REILD)

Delivery of excessive radiation to the normal liver parenchyma may result in REILD.

The risk of REILD may also be increased in patients with pre-existing liver disease. Consideration should be given to reducing the prescribed activity of SIR-Spheres Y-90 resin microspheres in the following clinical settings[1]:

- Reduced liver functional reserve due to steatosis, steatohepatitis, hepatitis or cirrhosis
- Elevated baseline bilirubin level
- Non-selective treatment of small tumor burden (< 5% liver involvement)
- Small liver volume (< 1.5 L)
- Prior hepatic resection
- Prior liver directed therapy

4.3 Radiation Pneumonitis

High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis. Limit radiation dose to ≤ 30 Gy per treatment and ≤ 50 Gy cumulatively. [*See Appendix III (Dosing and Administration Instructions)*].

4.4 Limited Radiation Dosimetry Planning Precision

The amount of radiation delivered to HCC targets has been found to differ compared to the amount planned *[see Clinical Trial Results (6.3)]*. 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 Appendix III (Dosing and Administration Instructions)*].

5 Precautions

5.1 Precautions for All Patients

- No studies have been done on the safety and effectiveness of this device in pregnant women, nursing mothers or children.
- Due to the radioactivity of this device and the significant consequences of misplacing the microspheres in situ, this product must be implanted by qualified healthcare professionals with adequate training in the handling and implantation technique for this device. [*See Appendix I (General Information)*].
- As a check on the quality of yttrium-90 delivery, a SPECT or PET scan of the upper abdomen can be performed immediately after implantation of SIR-Spheres Y-90 resin microspheres. The scan will detect Bremsstrahlung or positron annihilation radiation from the yttrium-90.
- This product is radioactive. The use of this device is regulated under Title 10 of the Code of Federal Regulations Part 35. These regulations must be followed when handling this device. [*See Appendix I (General Information)*].
- All persons handling, dispensing and implanting this device must be familiar with and abide by all applicable requirements governing therapeutic radioactive materials. Accepted radiation protection techniques should be used to protect staff when handling both the isotope and the patient.
- Some patients may experience gastric problems following treatment, but proton pump inhibitors (PPI) or histamine H2-receptor antagonists (H-2 blocking agents) may be used the day before implantation of SIR-Spheres Y-90 resin microspheres and continued as per the approved PPI or H-2 blocking drug prescribing information.
- Many patients experience abdominal pain immediately after administration of SIR-Spheres Y-90 resin microspheres and pain relief may be required. *[See Adverse Events (7.1)]*.
- SIR-Spheres Y-90 resin microspheres demonstrated a mild sensitization potential when tested dermally in an animal model.

5.2 Precautions for Patients with mCRC

[*See Precautions (5.1)*]

- The safety and effectiveness of SIR-Spheres Y-90 resin microspheres for treating patients with mCRC has been demonstrated using the recommended Body Surface Area (BSA) method for prescribed activity determination. The Empirical method is not recommended. For some patients, the Empirical method may result in excessive activity being prescribed. [See *Appendix III.1 (Dosing and Administration Instructions – mCRC Indication)]*.

5.3 Precautions for Patients with HCC

[*See Precautions (5.1)*]

- The safety and effectiveness of SIR-Spheres Y-90 resin microspheres for treating patients with HCC has been demonstrated using the recommended segmentectomy/partition method for prescribed activity determination. The BSA method is not recommended. [See *Appendix III.2 (Dosing and Administration Instructions – HCC Indication)]*.
- No efficacy or safety data from the DOORwaY^{90} study are available to support the use of the device in patients with Child-Pugh score B or C cirrhosis.

[1] Gil-Alzugaray et al. Hepatology, Vol 57, No. 3, 2013.

The following pre-treatment disease characteristics are considered high-risk; patients with HCC and these characteristics were excluded from pivotal testing [*See Clinical Trial Results (6.2)*]

- AST or ALT > 5 times the upper laboratory normal (ULN), platelet count < 100,000/microliter, WBC < 3 x 10^9/L, hemoglobin < 8.5 g/dL, international normalized ratio (INR) > 2.0, creatinine > 2 mg/dL, or glomerular filtration rate (GFR) < 50
- evidence for macrovascular invasion or < 30% of the total liver volume being disease-free
- maximal single tumor size > 8 cm or sum of the maximal tumor dimensions > 12 cm
- infiltrative tumor types or tumor nodules too numerous to count.

6 Clinical Trial Results

6.1 mCRC Indication

In a randomized, controlled clinical trial, a total of 70 patients were studied in two arms, 34 patients with FUDR chemotherapy (control group), and 36 patients with FUDR plus SIR-Spheres Y-90 resin microspheres. The results are shown in the following tables.

Table 1 – Tumor Response by Volume

Response	CR	PR	NC	PD	Others
FUDR only (N = 34)	1	7	12	9	5
FUDR + SIR-Spheres Y-90 resin microspheres (N = 36)*	2	16	10	5	3

*(P = 0.033)

Tumor response was measured by two consecutive CT scans in a 3-month interval period.

CR = Complete Response, PR = Partial Response, NC = No Change, PD = Progressive Disease, Others = No follow-up or unmeasurable

Table 1 indicates that there is a statistically significant improvement of the tumor response rates (CR+PR) in the group treated with FUDR plus SIR-Spheres Y-90 resin microspheres, when compared with the group treated with FUDR only.

Table 2 – Time to First Progressive Disease in the Liver

	FUDR Only	FUDR + SIR-Spheres Y-90 resin microspheres
Number of Patients	34	36
Mean Time in Days +/- SD*	312 Days +/- 330	510 Days +/- 516
Median Time in Days*	233 Days	366 Days

*(P = 0.05)

Progressive Disease was defined as more than 25% increase of tumor volume, or development of new lesion(s) in the follow up CT scan, when compared to the pre-treatment CT scan.

Table 2 indicates that there is a statistically significant delay of time to progression of the disease in the group treated with FUDR plus SIR-Spheres Y-90 resin microspheres, when compared with the group treated with FUDR only.

6.2 HCC Indication

The DOORwaY^{90} study — A prospective, multicenter, open-label single arm study evaluating the safety and efficacy of selective internal radiation therapy (SIRT) using SIR-Spheres® Y-90 resin microspheres on duration of response (DoR) and objective response rate (ORR) in unresectable hepatocellular carcinoma (HCC) patients

A total of 100 subjects were enrolled at 18 centers in the U.S. The mean subject age was 68.4 ± 10 years (range 33-91 years) and 75% were male. The most common pre-existing liver disease conditions were cirrhosis (48%) and NASH/NAFLD (22%). At baseline, 80% of subjects had early HCC (BCLC Stage A), 3% had advanced HCC (BCLC Stage C), and all subjects were Child-Pugh A, of which 79% were Child-Pugh A5. The 100 subjects had a total of 127 tumors, the majority of which (72.4%) were in the right lobe. Tumor sizes ranged from 0.3 to 8.0 cm (median 2.7 cm). A total of 13 tumors were in the largest size range (>5 cm to 8 cm).

The results of the study are shown in Table 3

Localized mRECIST outcomes were assessed for all 65 subjects whose response was adjudicated by the independent core laboratory (the DOORwaY^{90} effectiveness cohort).

Table 3 Response to SIR-Spheres Y-90 Resin Microspheres Treatment (DOORwaY^{90} Study)

Characteristics	Response (N = 65)	Confirmed Response (N = 65)
Overall response rate (ORR) through 9 months	98.5% (64/65) [88.6%, 100.0%]	90.8% (59/65) [77.0%, 97.7%]
Complete response (CR)	92.2% (59/64)	91.5% (54/59)
Partial response (PR)	7.8% (5/64)	8.5% (5/59)
Duration of response (DoR)		
N	64	59
Mean ± SD (days)	238.7 ± 106.9	258.9 ± 84.2
Median (range, days)	300.5 (0.0-375.0)	303.0 (51.0-375.0)
Percent with duration ≥ 6 months	76.6% (49/64)	83.1% (49/59)

The best ORR and confirmed ORR were 98.5% [99.3% CI: 88.6%, 100%] and 90.8% [99.3% CI: 77.0%, 97.7%], respectively. Median DoR was 300.5 days with 76.6% subjects exhibiting a DoR ≥6 months. Tumor response (mRECIST) was evaluated by independent central image review from a third-party oncology core laboratory.

6.3 Radiation Dosimetry Planning Precision

Y-90 SPECT/CT (N=79) or Y-90 PET/CT (N=21) imaging was acquired in all DOORwaY^{90} patients for exploratory analysis of differences between planned and delivered administered radioactivity (GBq) and HCC tumor absorbed dose (Gy). The results of this analysis are shown in Table 4

Table 4 –Radiation Dosimetry Planning Precision (DOORwaY^{90} Study)

Study patients (N=100[1]) in whom measured delivery was equal to the planned amount ± 20%:	Percentage (%) (95% confidence interval)
Administered activity (GBq)	71 (61,80)
Tumor absorbed dose (Gy)	18 (11,27)

[1] Of the 100 subjects and 137 Y-90 infusion sites analyzed, a subject was counted for the percentages shown if the measured delivery corresponding to each planned infusion site was equal to the planned activity (GBq) and tumor dose (Gy) ± 20%.

7 Adverse Events

7.1 All Patients

When the patient is treated with proper technique, without excessive radiation to any organ, the common adverse events after receiving the SIR-Spheres Y-90 resin microspheres are fever, transient decrease of hemoglobin, mild to moderate abnormality of liver function tests (mild increase in SGOT, alkaline phosphatase, bilirubin), abdominal pain, nausea, vomiting, and diarrhea.

Clinical side effects 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 SIR-Spheres Y-90 resin microspheres, may include the following:

Allergic reaction
Altered liver function, acute or chronic
Anorexia
Anxiety
Ascites
Bile Duct injury
Bleeding/hemorrhage
Chills / rigors
Cholecystitis (inflammatory or infectious)
Colitis
Death
Dehydration
Diarrhea
Dizziness
decompensation
Dyspnea
Edema (any location)
Electrolyte abnormalities
Elevated BUN/creatinine
Fall
Fatigue
Fever
Gastrointestinal bleeding/ hemorrhage
Gastrointestinal ulcer or ulceration
Hepatic encephalopathy
Hepatorenal failure
Hiccups
Hypertension
Hypotension
Infection (any location)
Liver failure, acute or chronic
Lymphopenia
Malaise
Mood alteration
Muscle weakness
Nausea
Neutropenia
Pain (any location)
Pancreatitis
Platelet count abnormalities
Pleural effusion
Pre-existing chronic liver disease
Portal hypertension
Pulmonary edema
Pulmonary fibrosis
Radiation hepatitis
Radiation induced disease, acute
Radioembolization Induced Liver Disease (REILD)
Sepsis
Supraventricular arrhythmia
Thrombosis (arterial or venous)
Tumor inflammation (including tumor edema)
Tumor-lysis syndrome
Vomiting
Weight loss

Complications related to the administration procedure itself may include:

Allergic reaction
Arterial injury including vessel dissection
Aspiration pneumonia
Bruising / bleeding / hematoma at site
Constipation / abdominal distension
Fatigue
Flushing
Infection
Nausea
Nerve damage
Pain (any location)
Vomiting

Potential Serious Adverse Events Due to High Radiation

***Acute pancreatitis*:** causes immediate severe abdominal pain. Verify by SPECT imaging of the abdomen (Yttrium-90 Bremsstrahlung image) and test for serum amylase.

***Radiation pneumonitis*:** causes excessive non-productive cough. Verify by X-ray evidence of pneumonitis.

***Acute gastritis*:** causes abdominal pain. Verify by standard methods to diagnosis gastric ulceration.

***Acute cholecystitis*:** causes significant upper abdominal pain and may require cholecystectomy for resolution. Verify by appropriate imaging studies.

***Radioembolization induced liver disease (REILD)*:** REILD is a rare complication following SIRT. REILD is characterized by a well-defined constellation of temporal, clinical, biochemical and histopathologic findings. It typically manifests approximately 4 to 8 weeks post-SIRT and is characterized clinically by

jaundice and ascites in the absence of tumor progression or bile duct obstruction.

The typical biochemical picture of REILD is an elevated bilirubin (> 3 mg/dL) in almost all cases, elevated alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) in most cases, accompanied by virtually no change in the transaminases (AST and ALT). In the event that a liver biopsy is performed, the typical histological appearance is of sinusoidal obstruction that may resemble veno-occlusive disease.

REILD may occur in both non-cirrhotic and cirrhotic patients.

Prophylactic treatment with methyl-prednisolone and ursodeoxycholic acid starting on the day of SIRT and continued for two months may reduce the incidence of REILD.

In the treatment of REILD, low molecular weight heparin may also be considered but both corticosteroids and heparin may only be useful if commenced very early in the course of the disease. [*See* Warnings *(4.2)]*.

7.2 Patients with mCRC

[See Adverse Events (7.1)]

The CRI9101 study— A controlled randomised trial comparing selective internal radiation therapy with hepatic perfusion chemotherapy

In the Phase III randomized controlled clinical trial with 70 patients, there was a minimal increase of Grade 1 and 2 events, mostly transient abnormal LFTs and nausea and vomiting in the patients who received SIR-Spheres Y-90 resin microspheres. There was no difference in the number of patients who developed Grade 3 and 4 adverse events between the two groups. No patient died due to the adverse events directly related to SIR-Spheres Y-90 resin microspheres.

Table 5 – CRI9101 Adverse Events

Events	Grade 1 and 2		Grade 3 and 4	
	FUDR	FUDR + SIR-Spheres Y-90 resin microspheres	FUDR	FUDR + SIR-Spheres Y-90 resin microspheres
Hemoglobin	4	5	1	0
Bilirubin	7	2	0	1
AST (SGOT)	110	109	14	7
Alk. Phos.	90	188	5	14
Nausea/ Vomiting	5	13	2	1
Diarrhea	6	3	1	0
TOTAL	**222**	**320**	**23**	**23**

The data in Table 5 are from a clinical trial with 34 patients on chemotherapy only, and 36 patients on chemotherapy plus SIR-Spheres Y-90 resin microspheres.

7.3 Patients with HCC

[See Adverse Events (7.1)]

The DOORwaY^{90} study — A prospective, multicenter, open-label single arm study evaluating the safety and efficacy of selective internal radiation therapy (SIRT) using SIR-Spheres® Y-90 resin microspheres on duration of response (DoR) and objective response rate (ORR) in unresectable hepatocellular carcinoma (HCC) patients

A total of 604 adverse events (AEs) were reported in 87 subjects out of 100 subjects, the majority of which (62.4%) were CTCAE grade 1. A total of 90 AEs were of moderate severity or higher (CTCAE grade 3 or higher), including 64 grade 3 AEs, 13 grade 4 AEs and 13 unrelated grade 5 (death) AEs. There were 89 serious adverse events (SAEs), of which 13 SAEs had an outcome of death; none was considered device-or-procedure-related. The most common cause of death was respiratory failure (4 subjects), followed by HCC or disease progression (3 subjects). The cause of death was unknown for 4 subjects. Four SAEs were both serious and device- and/or procedure-related, including two instances of abdominal pain, one instance of ascites* and one instance of nausea.

Table 6. DOORwaY^{90} All Adverse Events Occurring in ≥ 5% of Subjects by Frequency and Grade 3-4

Preferred Term (PT) by System Organ Class (SOC)	All Grades		Grades 3-4	
	% (n/N) of All AEs (N = 604)	% (n/N) of All Subjects (N = 100)	% (n/N) of All AEs (N = 604)	% (n/N) of All Subjects (N = 100)
Gastrointestinal disorders				
Abdominal pain	5.1% (31/604)	24.0% (24/100)	0.3% (2/604)	2.0% (2/100)
Nausea	3.8% (23/604)	17.0% (17/100)	0.2% (1/604)	1.0% (1/100)
Constipation	3.0% (18/604)	15.0% (15/100)	0.0% (0/604)	0.0% (0/100)
Vomiting	1.8% (11/604)	11.0% (11/100)	0.0% (0/604)	0.0% (0/100)
Ascites*	1.2% (7/604)	6.0% (6/100)	1.0% (6/604)	5.0% (5/100)
Abdominal distension	1.0% (6/604)	6.0% (6/100)	0.0% (0/604)	0.0% (0/100)
Diarrhoea	1.0% (6/604)	6.0% (6/100)	0.0% (0/604)	0.0% (0/100)
General disorders and administration site conditions				
Fatigue	7.5% (45/604)	39.0% (39/100)	0.0% (0/604)	0.0% (0/100)
Oedema peripheral	1.7% (10/604)	8.0% (8/100)	0.2% (1/604)	1.0% (1/100)
Metabolism and nutrition disorders				
Decreased appetite	3.3% (20/604)	19.0% (19/100)	0.2% (1/604)	1.0% (1/100)
Nervous system disorders				
Dizziness	1.8% (11/604)	8.0% (8/100)	0.0% (0/604)	0.0% (0/100)
Hepatic encephalopathy	1.3% (8/604)	7.0% (7/100)	0.5% (3/604)	3.0% (3/100)
Respiratory, thoracic and mediastinal disorders				
Cough	2.3% (14/604)	13.0% (13/100)	0.0% (0/604)	0.0% (0/100)
Dyspnoea	1.8% (11/604)	11.0% (11/100)	0.0% (0/604)	0.0% (0/100)
Respiratory failure	1.2% (7/604)	6.0% (6/100)	0.3% (2/604)	2.0% (2/100)
Investigations				
Weight decreased	1.7% (10/604)	8.0% (8/100)	0.0% (0/604)	0.0% (0/100)
Infections and infestations				
Corona virus infection	1.2% (7/604)	7.0% (7/100)	0.2% (1/604)	1.0% (1/100)
Musculoskeletal and connective tissue disorders				
Back pain	1.7% (10/604)	10.0% (10/100)	0.2% (1/604)	1.0% (1/100)
Injury, poisoning and procedural complications				
Contusion	1.2% (7/604)	6.0% (6/100)	0.0% (0/604)	0.0% (0/100)
Skin and subcutaneous tissue disorders				
Pruritus	1.3% (8/604)	7.0% (7/100)	0.0% (0/604)	0.0% (0/100)
Renal and urinary disorders				
Dysuria	0.8% (5/604)	5.0% (5/100)	0.0% (0/604)	0.0% (0/100)
Pollakiuria	0.8% (5/604)	5.0% (5/100)	0.0% (0/604)	0.0% (0/100)
Psychiatric disorders				
Insomnia	1.7% (10/604)	10.0% (10/100)	0.0% (0/604)	0.0% (0/100)
Blood and lymphatic system disorders				
Anaemia	1.2% (7/604)	6.0% (6/100)	0.0% (0/604)	0.0% (0/100)

*Post-data cut, the one serious, device related event of ascites was reassessed as REILD by the site investigator. The outcome of the event was "resolved."

Related AEs

In DOORwaY^{90} 29.0% (29/100) of subjects had a total of 53 AEs classified as related to either device or procedure, 26.0% (26/100) of subjects had a total of 43 AEs classified as related to device, and 23.0% (23/100) subjects had a total of 44 AEs classified as related to procedure.

Table 7. DOORwaY^{90} All Device Related Adverse Events by PT Frequency Occurring in ≥ 5% of Subjects

Preferred Term (PT)	% (n/N) of All Device Related AEs (N = 43)	% (n/N) of All Subjects (N = 100)
Abdominal pain	18.6% (8/43)	8.0% (8/100)
Vomiting	14.0% (6/43)	6.0% (6/100)
Nausea	11.6% (5/43)	5.0% (5/100)
Fatigue	25.6% (11/43)	11.0% (11/100)

Table 8. DOORwaY^{90} All Implant Procedure Related AEs by PT Frequency Occurring in ≥ 5% of Subjects

Preferred Term (PT)	% (n/N) of All Procedure Related (N = 44)	% (n/N) of All Subjects (N = 100)
Abdominal pain	20.5% (9/44)	7.0% (7/100)
Vomiting	13.6% (6/44)	6.0% (6/100)
Nausea	11.4% (5/44)	5.0% (5/100)
Fatigue	18.2% (8/44)	8.0% (8/100)

8 Pre-treatment Evaluation

8.1 All Patients

Appropriate imaging studies are recommended to determine the extent of disease, including the following:

- Hepatic angiogram.
- Technetium Tc 99m albumin aggregated (^{99m}Tc MAA) nuclear medicine scanning. The intraarterial (intrahepatic) catheter tip should be placed within 10 mm of the anatomical position from which the SIR-Spheres Y-90 resin microspheres will be administered. If a port has been inserted, this test can be performed through the port.

8.2 Patients with mCRC

[See 8.1]

When treating patients with mCRC with SIR-Spheres Y-90 resin microspheres when the extent of hepatic disease is considered non-resectable. In any of the following circumstances, patients would generally be considered non-resectable:

- Multiple liver metastases together with involvement of both lobes.
- Tumor invasion of the hepatic confluence where the three hepatic veins enter the IVC such that none of the hepatic veins could be preserved if the metastases were resected.
- Tumor invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken.
- Widespread metastases such that resection would require removal of more liver than is necessary to maintain life.

Resectability may be evaluated via imaging with a triple phase contrast angio-portal CAT scan or MRI.

9 Radiation Safety

The preparation and implant procedure involve potentially serious radiation exposure and contamination hazard to the staff. All requirements for microsphere brachytherapy must be followed concerning implantation and post-implantation care.

The following are sample measured thermoluminescent dosimetry (TLD) exposures to personnel.

Table 9 – Exposure Dose per Patient for Implant Preparation (Technologist)

	Trunk mSv (mrem)	Lens of the Eye mSv (mrem)	Hands mSv (mrem)
Shallow Dose (0.07mm)	0.027 (2.7)	0.026 (2.6)	0.35 (35)
Deep Dose (10 mm)	0.003 (0.3)	0.004 (0.4)	

Assuming handling of a 3 GBq device and dose preparation time of 30 minutes. TLDs were worn near the pelvis, on the shirt's lapel, and on the working finger.

Table 10 – Exposure Dose per Patient for Implant Procedure (Physician)

	Trunk mSv (mrem)	Lens of the Eye mSv (mrem)	Hands mSv (mrem)
Shallow Dose (0.07mm)	0.038 (3.8)	0.12 (12)	0.32 (32)
Deep Dose (10 mm)	0.004 (0.4)	0.054 (5.4)	

Assuming average patient dose of approximately 2 GBq and dose injection time of 20 minutes.

Post-Implant Exposure
Exposure data from patients implanted with an average of 2.1 GBq at approximately 5-6 hours post implantation at the following distances from the patient's abdomen:

Table 11 – Post Implant Exposure

Distance	Exposure
0.25 m	18.8 mSv/hr
0.5 m	9.2 mSv/hr
1.0 m	1.5 mSv/hr
2.0 m	0.4 mSv/hr
4.0 m	<0.1 mSv/hr

(1 mSv = 0.1 mrem)

10 How Supplied

SIR-Spheres Y-90 resin microspheres are provided in a vial with water for injection. Each SIR-Y001 vial contains 3 GBq of Y90 ± 10% (at the time of calibration) in a total of 5 cc water for injection and contains 40 – 80 million microspheres. Each SIR-Y002 vial contains 1.8 GBq of Y^{90} ± 10% (at the time of calibration) in a total of 3 cc water for injection and contains 24 – 48 million microspheres. The vial is shipped within a 6.4 mm minimum thickness lead pot. The package consists of a crimp-sealed SIR-Spheres Y-90 resin microspheres glass vial within a lead pot, and a package insert within Type-A packing bucket.

The vial and its contents should be stored inside its transportation container at room temperature (15-25 °C, 59-77 °F).

The calibration date (for radioactive contents) and the expiration information are quoted on the vial label. The useful life of the SIR-Spheres Y-90 resin microspheres ends 24 hours after the time of calibration. The particle size has been tested prior to shipment,to have less than 2% of particles smaller than 24 µm and less than 10% of particles larger than 34 µm.

11 Appendices

Appendix I: General Information

Restricted to Accredited Facilities
SIR-Spheres Y-90 resin microspheres may only be dispatched to a duly licensed or accredited facility capable of handling therapeutic medical isotopes.

Distribution to Trained and Licensed Healthcare Professionals
This device is for distribution to persons licensed pursuant to 105 CMR 120.589 or under equivalent licenses of the Nuclear Regulatory Commission, an Agreement State, or a licensing State. Only healthcare professionals qualified and licensed under Title 10 Code of Federal Regulations Part 35 (Nuclear Regulatory Commission) and trained under the Sirtex TEC training program may order and implant SIR-Spheres Y-90 resin microspheres.

Appendix II: Treatment Preparation Procedure

Unpacking:
- Unpack SIR-Spheres Y-90 resin microspheres, leaving shipping vial in lead pot.
- Place on the bench top in a lead or acrylic shielded box if available.
- Remove the center of aluminum seal from sterile Delivery vial with forceps and clean the septum with an alcohol swab.
- Place the Delivery vial in the acrylic holder or transport base for stability and shielding.

Vent Process:
- Insert a short 25-gauge needle through the septum of the Delivery vial until it just pierces the septum to create a vent

Priming:
- Consult the Class I SIROS Delivery System instructions for use for detailed priming information.

Drawing the Patient-Specific Activity Process
- Invert the lead pot and shake vigorously before opening to re-suspend the SIR-Spheres Y-90 resin microspheres, which will have settled during shipping.
- Quickly open the lead pot and remove the shipping vial using forceps.
- Determine the total activity of SIR-Spheres Y-90 resin microspheres in the shipping vial using an appropriate ion chamber (dose calibrator) and then return the shipping vial to the lead pot.
- Determine the volume of SIR-Spheres Y-90 resin microspheres suspension that needs to be withdrawn from the shipping vial to provide the intended patient-specific activity of SIR-Spheres Y-90 resin microspheres. Partially remove the aluminum seal of the SIR-Spheres Y-90 resin microspheres shipping vial, clean with alcohol swab.
- Insert a 25-gauge needle through the septum of the shipping vial to create a vent, ensuring the needle is well clear of the contents in the shipping vial.
- Use a shielded 5 ml syringe with a 21-gauge hypodermic needle at least 50 mm long to puncture the septum of the SIR-Spheres Y-90 resin microspheres shipping vial, and quickly draw back and forth several times in order to mix the SIR-Spheres Y-90 resin microspheres thoroughly.
- Quickly withdraw the pre calculated patient radiation dose, and transfer into the vented Delivery vial. Withdraw the required amount quickly before the contents of the shipping vial start to settle.
- Verify the patient dose in the Delivery vial by re-measuring the activity in the shipping vial with dose calibrator, and correct, if necessary.
- Add the pre-calculated additional volume of sterile water or D5W.

Secure top of the dedicated holder onto the Delivery vial.
The patient dose is now ready for transport to the SIR-Spheres Y-90 resin microspheres implantation room.

Appendix III: Dosing and Administration Instructions

III.1. mCRC Indication

The recommended method for calculating the individual patient dose is the Body Surface Area (BSA) method.

The safety profile of the prescribed activity equations that enable accurate lobar treatment with SIR-Spheres Y-90 resin microspheres is well established. The BSA method can take into account the volume of a single treated lobe, as well as that of the entire liver.

In this respect, the approach of lobar treatment versus whole liver treatment with SIR-Spheres Y-90 resin microspheres is based on the presence of visible tumors on pre-treatment CT or MR imaging. If liver tumors are only visible in one lobe, then SIR-Spheres Y-90 resin microspheres should be administered to that lobe only, thus sparing the contralateral lobe from unnecessary internal radiation.

Use of dosimetry formulas
BSA must first be determined and is calculated from the following equation (Equation 1):

$$BSA\ (m^2) = 0.20247 \times height(m)^{0.725} \times weight(kg)^{0.425}$$

Prescribed activity calculation for whole liver / bilobar treatment

$$\textit{Prescribed activity of SIR-Spheres Y-90 resin microspheres (GBq)} = (BSA - 0.2) + \left(\frac{V_{tumor}}{V_{tumor} + V_{normal\ liver}}\right)$$

Where:
V_{tumor} is the total volume of tumor in the liver
$V_{normal\ liver}$ is the volume of the non-tumor liver tissue

Prescribed activity calculation for lobar or super-selective treatment
In patients who receive lobar or segmental treatment with SIR-Spheres Y-90 resin microspheres the prescribed activity must be reduced in accordance with the size of the portion of the liver being treated.

$$Activity_L\ (GBq) = \left[BSA - 0.2 + \left\{\frac{Tumor\ volume_L}{Total\ volume_L}\right\}\right] \times \left[\frac{Total\ volume_L}{Total\ liver\ volume}\right]$$

Where:
Activity$_L$ is the prescribed activity for the lobe
Tumor volume$_L$ is the volume of tumor present in the lobe
Total volume$_L$ is the total volume of the lobe including the tumor in the lobe
Total liver volume is the total volume of the liver including the tumor
BSA is the Body Surface Area as per Equation 1

Lung Shunt Calculation Procedure
- Inject 4 mCi (148 MBq) of ^{99m}Tc MAA into the hepatic artery via a catheter
- Use a large FOV gamma camera, and obtain anterior and posterior images of the chest and abdomen (with 700 k to 1 million counts on abdomen, and the same count on the chest)
- Take right lateral abdomen, using same count
- Draw ROI around the whole liver and the whole lung and get the total counts for the lung and the liver
- Calculate the % shunt using following formula:

$$\%\ Shunt = \left(\frac{Lung\ Counts}{Liver\ Counts + Lung\ Counts}\right) \times 100$$

In order to optimize the risk/benefit for patients receiving SIR-Spheres Y-90 resin microspheres, limiting the radiation exposure to the lungs to

≤ 30 Gy is required. The calculation of estimated radiation exposure to the lungs is given by the following formulae:

Activity that may potentially reach the lung:

$$A_{lung}\ (GBq) = A_{total}\ \times L/100$$

Where:
A_{lung} = lung activity (GBq)
A_{total} = total prescribed activity (GBq)
L = lung shunt (%)

The resulting lung dose, given that a given amount of activity shunts from the liver to the lung:

$$D_{lung}\ (Gy) = \frac{49670 \times A_{lung}}{M_{lung}}$$

Where:
D_{lung} = lung dose (Gy)
A_{lung} = lung activity (GBq)
M_{lung} = mass of the lung (g)

Example of prescribed activity calculation for right lobe treatment

Total liver volume = 1,800 mL
Total right lobe volume including tumor = 1,200 mL
Tumor volume in the right lobe = 300 mL
BSA = 2.0 m^2
Liver-lung shunt = 20%
Lung Mass = 1000 g

$$Prescribed\ activity\ for\ the\ right\ lobe\ (GBq)$$
$$= \left[2.0 - 0.2 + \left\{\frac{300}{1{,}200}\right\}\right] \times \left[\frac{1{,}200}{1{,}800}\right] = \mathbf{1.37\ GBq}$$

In this example, given the lung shunt = 20%, pulmonary radiation exposure is taken into consideration:

$$A_{lung}\ (GBq) = 1.37\ GBq\ \times 20/100\ = \mathbf{0.274\ GBq}$$

Given that 0.274 GBq shunts from the liver to the lung, the resulting lung dose is:

$$D_{lung}\ (Gy) = \frac{49670 \times 0.274}{1000\ g}\ = \mathbf{13.6\ Gy}$$

A pulmonary radiation exposure of 13.6 Gy is less than the 30 Gy established limit, therefore no reduction in prescribed activity would be required.

III.2. HCC Indication

Recommended Dose (Segmentectomy/Partition Method)

When planning for a radiation segmentectomy, the recommended radiation absorbed dose to the target liver segment is 150 Gy to 400 Gy. Recommended normal tissue constraints are 30 Gy per treatment and 50 Gy cumulatively to the lungs.

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 150 Gy to 400 Gy. Recommended normal tissue constraints are 150 Gy to the perfused normal liver, 30 Gy per treatment, and 50 Gy cumulatively to the lungs.

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 about 4 mCi (148 MBq) of ^{99m}Tc MAA via a catheter with the tip placed within 10 mm of the anatomical position from which the SIR-Spheres Y-90 resin 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 (L) using the following formula:

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

Activity that may potentially reach the lung:

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

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

Activity Calculation

The recommended segmentectomy/partition method requires two types of measurement:

1. Measurement of the perfused target volume (partition1) and, when planning to perfuse multiple liver segments, measurement of the perfused normal liver volume (partition2). Otherwise, for a segmentectomy, the partition2 volume is zero. Partition volume(s) should be determined from cross-sectional anatomical imaging.
2. Measurement of lung counts should be based on planar ^{99m}Tc MAA imaging. Measurement of partition(s) counts should be based on ^{99m}Tc MAA SPECT imaging.

To calculate the activity to be implanted, it is necessary to:

1. Calculate the partition(s) volume. Convert from volume to mass on the basis of 1.06 g/cc.
2. Using the ^{99m}Tc MAA imaging, determine the counts in the lung and perfused liver partition(s) volumes.

For segmentectomy, the tumor to normal liver ratio (TNR) is defined as 1. Otherwise, when planning to perfuse multiple liver segments, determine TNR using the following equation:

$$TNR = \frac{A_{partition1}/M_{partition1}}{A_{partition2}/M_{partition2}}$$

$$= \frac{\text{average counts per ml in partition1}}{\text{average counts per ml in partition2}}$$

Where:
$A_{partition1}$ = Activity or counts in perfused tumor volume
$M_{partition1}$ = Mass of perfused tumor volume
$A_{partition2}$ = Activity or counts in perfused normal liver volume
$M_{partition2}$ = Mass of perfused normal liver volume

To calculate the total activity to be implanted, use the following equations.

$$\mathrm{A}_{Admin} = \frac{D_{target}\,(M_{target} + M_{normal}/TNR)}{49670 * (1 - L)}$$

Where:
A_{Admin} = SIR-Spheres activity to implant [GBq]
D_{target} = Desired absorbed dose to perfused target volume [Gy] [*See Appendix IV (IV.1)*]
M_{target} = Mass of perfused target volume [g]
M_{nomral} = Zero for segmentectomy; otherwise, mass of perfused normal liver volume [g].

When planning to perfuse multiple liver segments:

$$D_{normal} = D_{target}/TNR$$

Where:

D_{normal} = Mean absorbed dose to perfused normal liver volume [Gy].

To determine the lung dose, given that a fraction of activity shunts from the liver to the lung:

$$D_{lung}\ = \frac{49670 \times A_{Admin} \times L}{M_{lung}}$$

Where:
D_{lung} = lung dose [Gy]
M_{lung} = mass of the lung [g]

The lung mass may be estimated from patient-specific CT scans[2] or as 1000 g[3].

Appendix IV: Intra-hepatic Technetium MAA Radiation Absorbed Doses

For complete Technetium Tc 99m albumin aggregated (^{99m}Tc MAA) prescribing information, refer both to the current medical imaging agent prescribing information and to this device labelling.

The recommended activity for intra-hepatic administration of ^{99m}Tc MAA is 4 mCi (148 MBq).

Estimated mean absorbed dose per activity (mGy/BGq) to whole body, liver and non-critical organs presented in Table 12 and the whole body effective dose is presented in Table 13.

Table 12 – Estimated Mean Organ and Whole Body Radiation Absorbed Doses from Intra-Hepatic ^{99m}Tc-MAA injection[1]

Region	Mean Absorbed Dose (mGy)	Mean Absorbed Dose per Activity (mGy/GBq)	
	Mean ± SD	Mean ± SD	Median (range)
Adrenal glands	1.38 ± 1.49	8.71± 8.77	6.42 (2.78 - 24.04)
Gallbladder	4.82 ± 4.92	31.67 ± 31.42	23.40 (3.29 - 76.58)
Heart	0.89 ± 0.73	5.68 ± 4.23	3.083 (2.12 - 11.51)
Kidney	2.14 ± 3.38	13.31 ± 20.15	4.14 (3.59 - 49.34)

[2] Kappadath SC, Lopez BP, Salem R, Lam MG. Lung shunt and lung dose calculation methods for radioembolization treatment planning. Q J Nucl Med Mol Imaging. 2021 Mar;65(1):32-42.

[3] ICRP, 2015. Radiation Dose to Patients from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances. ICRP Publication 128. Ann. ICRP 44(2S).

Liver Outside Treatment Zone	2.80 ± 2.18	17.96 ± 12.64	13.46 (4.82 - 38.31)
Liver Within Treatment Zone	19.64 ± 13.23	127.56 ± 80.59	156.02 (17.46 - 219.28)
Lungs	1.95 ± 2.01	12.37 ± 11.76	8.45 (2.92 - 32.89)
Pancreas	1.10 ± 0.91	6.99 ± 5.22	6.10 (3.21 - 15.90)
Spleen	0.81 ± 1.03	5.10 ± 6.02	1.65 (1.61 - 12.05)
Stomach	1.72 ± 1.72	10.92 ± 10.12	7.07 (3.03 - 27.35)
Upper bowel	0.86 ± 0.72	5.49 ± 4.19	4.78 (2.05 - 12.53)
Whole Body	0.96 ± 0.87	6.13 ± 5.06	4.97 (1.75 - 14.82)

1. Administered activity was approximately 150MBq for each subject; this value, which is not organ-specific, reflects the total dose to the subject and is used as the denominator for calculations of mGy/GBq shown in the table.

Table 13 – Whole Body Effective Dose

Region	Effective Dose (mGy)
Whole Body	N=5
Mean ± SD	0.6 ± 0.6
Median (range)	0.5 (0.0-1.5)

Appendix V: Correction for Decay

The physical half-life of yttrium-90 is 64.1 hours. Radioactive decay factors should be applied at the time of patient dose preparation, in order to calculate the true value of radioactivity present.

Table 14 – Decay Factors of SIR-Spheres Y-90 resin microspheres

Hours	Decay Factor
0.5	0.995
1	0.989
2	0.979
3	0.968
4	0.956
5	0.947
6	0.937
7	0.927
8	0.917
9	0.907
10	0.898
11	0.888
12	0.878
24	0.772
36	0.678
48	0.595
72	0.459

Caution: The time of the initial calibration must be converted to the user's local time.

Appendix VI: Symbols Definition Glossary Table

Symbol	Symbol Definition
	Manufacturer
	Date of manufacture
	Consult instructions for use
	Caution
	Use-by-date
	Lot or batch code
	Catalog number
	Serial number
	Quantity
	Sterilized using irradiation
	Sterilized using steam
	Ionizing radiation
	Single Use Only. Indicates a medical device that is intended for use on a single patient during a single procedure.

Symbol	Symbol Definition
	Do not resterilize
	Product is not made with natural rubber latex
	Do not use if package is damaged
	Keep dry
	Temperature limit
	Caution: Federal law (USA) restricts this device to sale by or on the order of a physician or licensed healthcare practitioner.
	Single sterile barrier system
	Medical device
	Unique Device Identifier
	Single sterile barrier system with protective packaging outside
	MR safe

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SIR-Spheres microspheres and SIR-Spheres Y-90 resin microspheres are the terms used to describe the same device.