Boston Scientific
Advancing science for life™

THERASPHERE™
Y-90 Glass Microspheres

Dose Matters.

Power. Embedded Within.

Personalized

TheraSphere by design gives you **maximum flexibility** to deliver a highly potent dose across treatment approaches

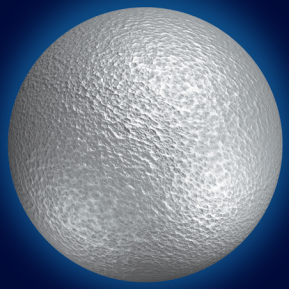
The power of TheraSphere starts with its unique design. Inactive Yttrium-89 is combined with aluminum oxide and silicon oxide into tiny glass microspheres. Neutron bombardment transforms the inactive Y-89 trapped inside each sphere into radioactive Y-90. Because the Yttrium is embedded within the glass matrix, and not surface-bound like resin microspheres[1], each TheraSphere glass microsphere has unmatched radioactive concentration.

RADIATION PERMEATES GLASS SPHERES

TheraSphere Y-90 Glass Microsphere

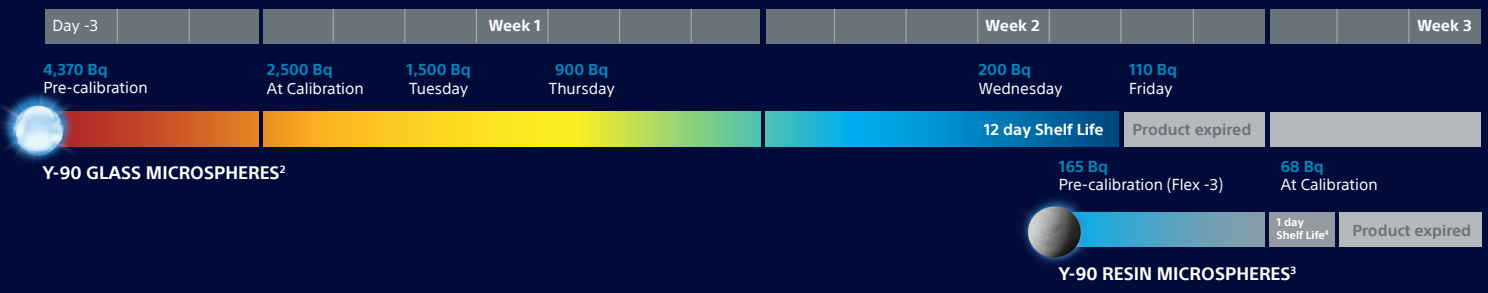
Radiation dose is embedded within the whole of the glass matrix, providing greater Y-90 loading capacity

Y-90 Resin Microsphere



Radiation dose is only coated onto the surface area of a resin sphere[1], limiting Y-90 loading capacity

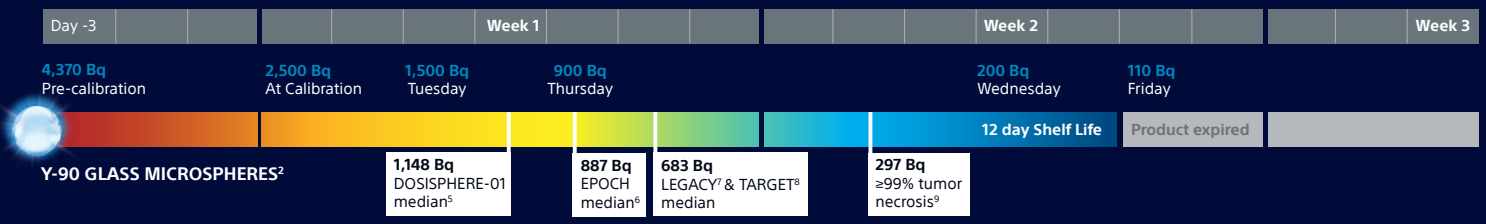
GLASS MAINTAINS A HIGHER RADIATION DOSE OVER TIME



Timepoint	Specific Activity (SA) Bq/sphere	
	TheraSphere™ Y-90 Glass Microspheres	Y-90 Resin Microspheres[3,4]
Day -3	4,370	165
Calibration	2,500	68
2nd week Wednesday	200	n/a (product expired)
2nd Week Friday	110 - product expired	n/a (product expired)

TheraSphere™ is indicated for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter), in patients with unresectable hepatocellular carcinoma (HCC), Child- Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status. SIR-Spheres® is indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

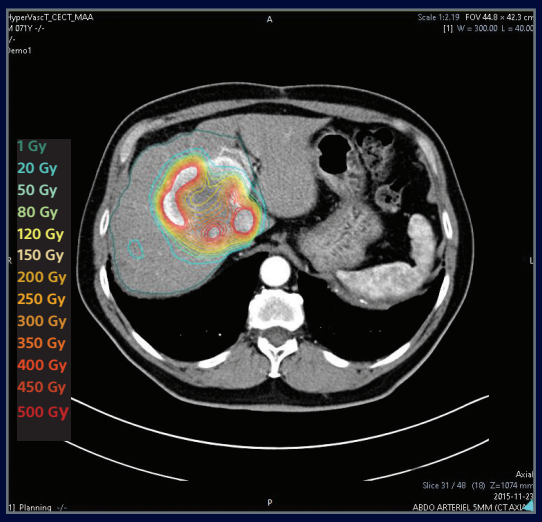
SPECIFIC ACTIVITY ACROSS THERASPHERE Y-90 GLASS MICROSPHERES CLINICAL STUDIES



CAUTION: Therasphere is under an investigational device exemption for treatment of patients with metastatic colorectal cancer. The safety and effectiveness for this treatment has not been established.

PERSONALIZED DOSIMETRY

TheraSphere is the only radiation therapy with Level 1 randomized data to demonstrate efficacy in large tumors (mean tumor size of 10.5 cm)[5], while also **validating reproducible dosimetry planning with Simplicit^{90}Y™ Personalized Dosimetry Software[10].**



Simplicit^{90}Y personalized dosimetry software, **developed exclusively for TheraSphere Y-90 Glass Microspheres**, allows you to enhance the consistency and efficiency of your dosing calculations. Visualize prospective dose distribution and assess the absorbed dose delivered to give you optimal versatility and control to calculate with confidence.

Precise

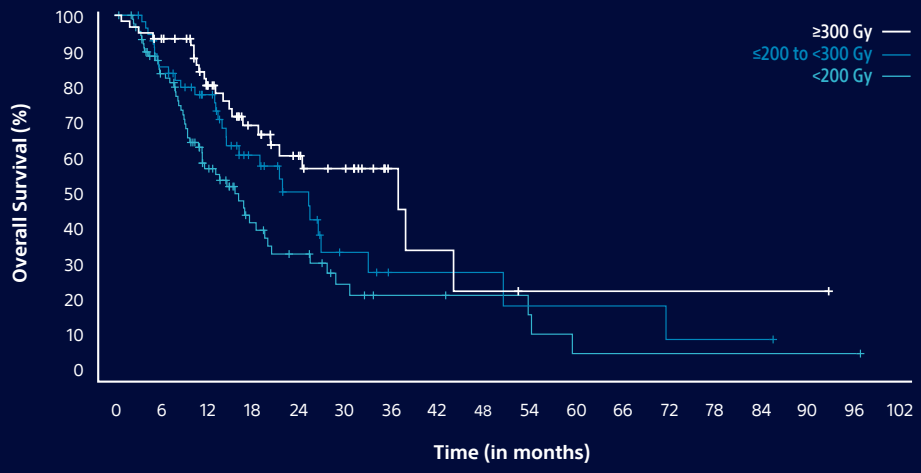
TheraSphere gives you the **most control** of any locoregional therapy for the treatment of HCC Liver Tumors[11]

THE OPTIMAL COMBINATION OF **ABSORBED DOSE AND SAFETY** TO NORMAL TISSUE

TheraSphere is the only Y-90 that has demonstrated:

- Tumor aborbed dose >225 Gy (lobar treatment) associated with 17% higher response[10]
- Segmentectomy dose ≥ 400 Gy associated with complete pathological necrosis[12] as shown with a subset of patients from the LEGACY Study
- No correlation between normal tissue absorbed dose and impact on safety* could be demonstrated in the TARGET Study.[10]

TARGET STUDY I Perfused Tumor Absorbed Dose by Subgroups

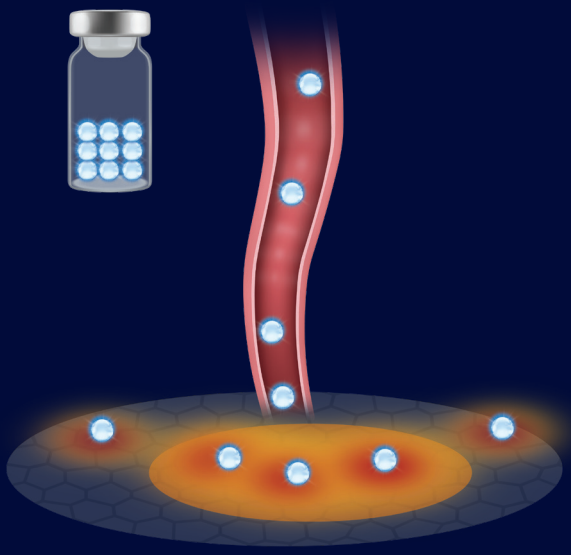


* ≥ GRADE 3 HYPERBILIRUBINEMIA

GLASS DELIVERS **UNIFORM DOSING** WITH LOW LIVER TOXICITY[13, 8]

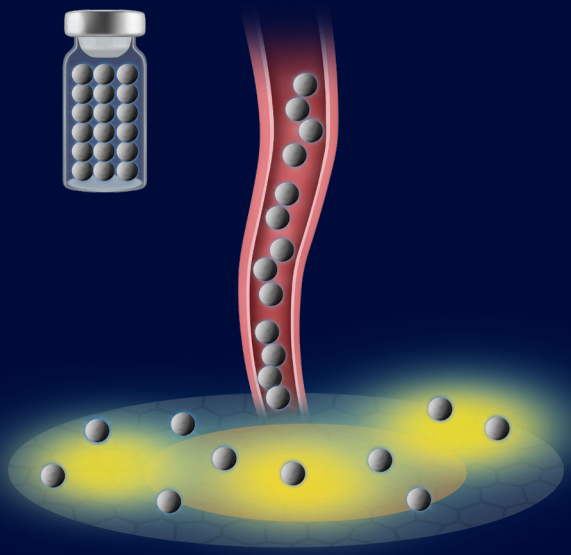
Pre-clinical study confirmed there is a substantial difference in absorbed-dose homogeneity and decreased normal liver toxicity for treatments at or before 8-days post-calibration.[13]

Day 4



Hetergenous concentration of particles in normal tissue

Day 12



More homogenous distribution of particles to normal tissue

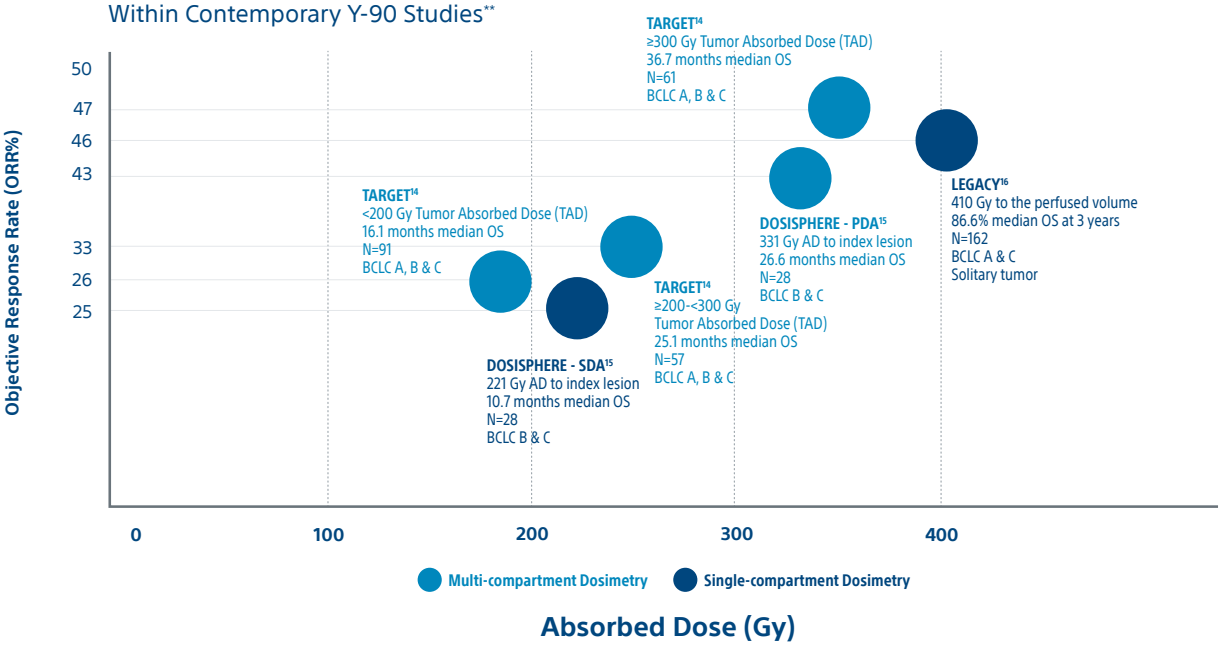
Proven

TheraSphere **demonstrates** tumor absorbed dose to overall tumor response and survival correlation

Key notable trials, DOSISPHERE-01 and TARGET confirmed the importance of optimal dosing and the correlation between **high tumor response and overall survival** benefit.

ABSORBED DOSE AND RESPONSE (RECIST 1.1) RELATIONSHIP: GLASS

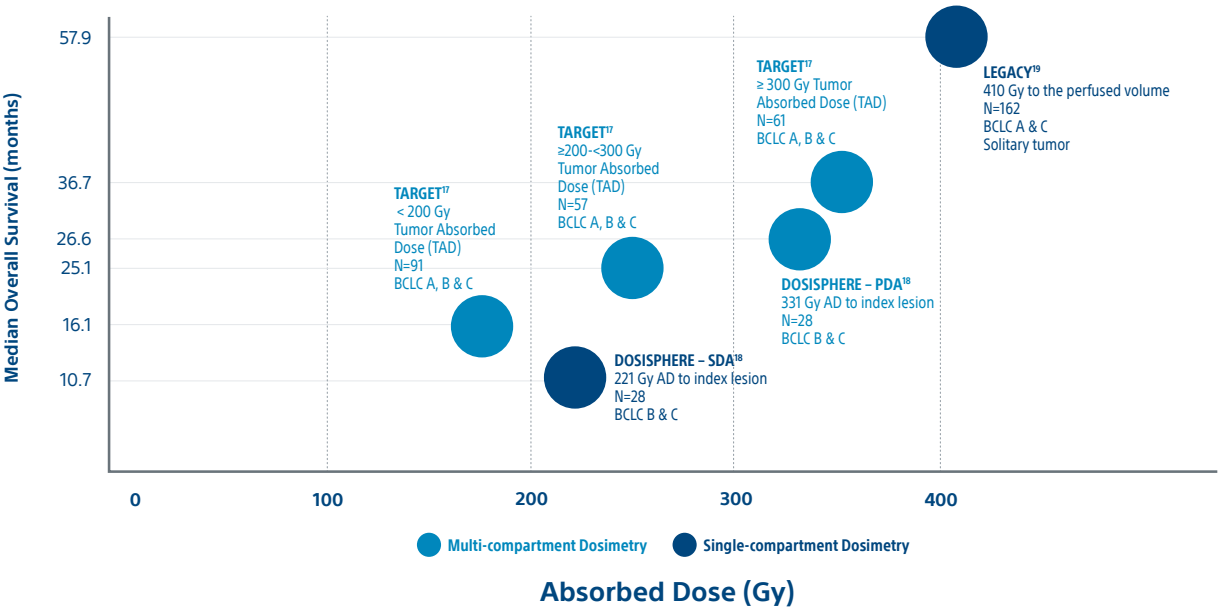
Within Contemporary Y-90 Studies**



DOSISPHERE-01 demonstrated a 16-month **improvement of overall survival** in advanced HCC patients who received a personalized TheraSphere dose as compared to the control arm.

ABSORBED DOSE AND OVERALL SURVIVAL RELATIONSHIP: GLASS

Within Contemporary Y-90 Studies**



** Studies not designed for head-to-head comparisons

Contact your TheraSphere Consultant or visit **www.TheraSphere.com** to learn more

1. Grosser OS, Ruf J, Pethe A, Kupitz D, Wissel H, Benckert C, Pech M, Ricke J, Amthauer H. Urinary Excretion of Yttrium-90 after Radioembolization with Yttrium-90-Labeled Resin-based Microspheres. Health Phys. 2018 Jan;114(1):58-63. doi: 10.1097/HP.0000000000000734. PMID: 29049048.
2. TheraSphere™ Y-90 Glass Microspheres IFU. Data on file.
3. Sirtex SIR-Spheres® FLEXdose Delivery Program https://www.sirtex.com/media/168730/flexdose-brochure_singlpg-apm-us-018-07-20-v3.pdf.
4. SIR-Spheres® Y-90 Resin Microspheres IFU https://www.sirtex.com/ media/169247/ssl-us-14-sir-spheres-microspheres-ifu-us.pdf.
5. TheraSphere™ Y-90 Glass Microspheres DOSISPHERE-01 Study. Data on file.
6. TheraSphere™ Y-90 Glass Microspheres EPOCH Study. Data on file.
7. TheraSphere™ Y-90 Glass Microspheres LEGACY Study. Data on file.
8. TheraSphere™ Y-90 Glass Microspheres TARGET Study. Data on file.
9. Toskich B, et.al. Pathologic Response of Hepatocellular Carcinoma Treated with Yttrium-90 Glass Microsphere Radiation Segmentectomy Prior to Liver Transplantation: A Validation Study. J Vasc Interv Radiol. 2021 Apr;32(4):518-526.e1.
10. Lam, Marnix. A Global Study of Advanced Dosimetry in the Treatment of Hepatocellular Carcinoma with Yttrium-90 Glass Microspheres: Analyses from the TARGET Study. Presented at SIR. March 25, 2021.
11. Dose distribution in radioembolization: a comparison between glass and resin microspheres. S. Young, S. Flanagan, D. D'Souza, J. Golzarian, J. Pontolillo, T. Chen, P. Sharma, J. Owen, P. Moran, T. Sanghvi; University of Minnesota; University of Minnesota Medical Center; Minneapolis VA. Abstract No. 445. 2020 SIR JVIR supplement.
12. Gabr A, Riaz A, Johnson GE, et al. Correlation of Y90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: confirmatory multicenter analysis in 45 explants. Eur J Nucl Med Mol Imaging. 2020 August 4;: p. doi: 10.1007/s00259-020-04976-8.
13. Pasciak, A. S., Abiola, G., Liddell, R. P., Crookston, N., Besharati, S., Donahue, D., Thompson, R. E., Frey, E., Anders, R. A., Dreher, M. R., & Weiss, C. R. (2019). The number of microspheres in Y90 radioembolization directly affects normal tissue radiation exposure. European Journal of Nuclear Medicine and Molecular Imaging, 47(4), 816–827. https://doi.org/10.1007/s00259-019-04588-x.
14. ORR measured in total perfused tumor by mRECIST, 70.8% ORR for the target lesion and 61.7% ORR for all lesions. Lam, Marnix. A Global Study of Advanced Dosimetry in the Treatment of Hepatocellular Carcinoma with Yttrium-90 Glass Microspheres: Analyses from the TARGET Study. Presented at SIR. March 25, 2021.
15. Standard dosimetry arm (SDA) in DOSISPHERE received 120 +/- 20 Gy to the perfused lobe. Personalized dosimetry arm (PDA) had goal of >/= 205 Gy to the index lesion, 250-300 Gy if possible and limit non-tumor tissue dose to </= 120 Gy. Response and survival measured in modified intent to treat (ITT) population. Garin E, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021;6(1):17-29. doi:10.1016/S2468-1253(20)30290-9.
16. LEGACY reported three-year survival rate of 86.6%. Primary confirmed response rate of 72.2% by mRECIST and 46.3% by RECIST 1.1 and best response rate of 88.3% by mRECIST. Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, Fowers K, Lewandowski R, Padia SA. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable Hepatocellular Carcinoma: The LEGACY Study. Hepatology. 2021 Mar 19. doi: 10.1002/hep.31819.
17. Lam, Marnix. A Global Study of Advanced Dosimetry in the Treatment of Hepatocellular Carcinoma with Yttrium-90 Glass Microspheres: Analyses from the TARGET Study. Presented at SIR. March 25, 2021. 70.8% ORR for the target lesion and 61.7% ORR for all lesions and best response rate of 88.3% by mRECIST." after RECIST 1.1.
18. Standard dosimetry arm (SDA) in DOSISPHERE received 120 +/- 20 Gy to the perfused lobe. Personalized dosimetry arm (PDA) had goal of >/= 205 Gy to the index lesion, 250-300 Gy if possible and limit non-tumor tissue dose to </= 120 Gy. Survival and response were measured in the intention to treat (ITT) and modified (mITT) populations. Mean Absorbed Dose to perfused liver was 331.1±131.5 for PDA Arm, and 221.3±139.4 for SDA Arm. Garin E, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021;6(1):17-29. doi:10.1016/S2468-1253(20)30290-9.
19. LEGACY reported three-year survival rate of 86.6%. Primary confirmed response rate of 72.2% by mRECIST and 46.3% by RECIST 1.1. Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, Fowers K, Lewandowski R, Padia SA. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable Hepatocellular Carcinoma: The LEGACY Study. Hepatology. 2021 Mar 19. doi: 10.1002/hep.31819.

TheraSphere™ Yttrium-90 Glass Microspheres

INDICATION FOR USE: TheraSphere is indicated for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in 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 is 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 16.5 mCi (0.61 GBq) of Y-90 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,O2) of < 60 mmHg, or oxygen saturation (Sa,O2) of < 90%) or severe liver dysfunction, including hepatic encephalopathy, clinically evident ascites or treatment with diuretics for ascites • 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 • with comorbidities or poor overall health (e.g., 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. Keep the TheraSphere dose vial upright and stored in its lead pot before and during patient treatment, except as required for radiation measurement. Do not open the dose vial acrylic shield prior to patient treatment. Post-treatment, waste materials require caution to prevent contamination and beta shielding due to residual glass microspheres. **PRECAUTIONS:** GENERAL PRECAUTIONS: As in any intra-arterial procedure, aseptic technique should be practiced, and care should be taken to ensure minimum patient anesthesia exposure extraneous to therapeutic objective. • Consideration of patient comorbidities should be used when determining the type and volume of fluid to infuse via catheter to avoid electrolyte imbalance, fluid shift, and hyperglycemia. • It is important to avoid any aggressive arterial procedure that may lead to arterial spasm that impairs TheraSphere distribution into the perfused liver target volume which may lead to underdosing or non- target deposition of TheraSphere. PRECAUTION IN PATIENTS WITH IMPAIRED LIVER FUNCTION: No efficacy or safety data from the LEGACY study are available to support the use of the device in patients with Child-Pugh score B or C cirrhosis. PRECAUTION IN VULNERABLE PATIENTS: No effectiveness or safety data are available to support the use of the device in children or breast- feeding women. ENDOCRINE DISRUPTION, CARCINOGENICITY, MUTAGENICITY, TOXICITY TO REPRODUCTION: Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses. RADIATION SAFETY: Radioactive products should be used only by healthcare professionals who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides. • As in the use of any radioactive material, ensure minimum radiation exposure to the patient extraneous to the therapeutic objective, and to minimize radiation exposure to workers and others in contact with the patient. RELEASE AND POST-TREATMENT PRECAUTIONS: Post treatment patient care: use universal precautions for body fluid contact. Trace Y-90 may be detectible in blood and urine; handle with gloves and dispose as normal body fluids. The radiation field is expected to be less than 1 mrem/h (10 µSv/h) at 3 ft (1 m) from the patient's abdomen. Supplemental shielding and segregation of the patient are not required to maintain exposure to others below regulated limits. • Release instructions: 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 1 ft (0.3 m) 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 (e.g., international travel). • Special precautions post-administration: 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 Y-90 TheraSphere implant. The physician should consult their radiation safety staff for handling and disposal of liver tissue. • Special liver tissue handling: 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. **POTENTIAL 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. 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 TheraSphere, 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 • 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 • Portal hypertension • Pre-existing chronic liver disease decompensation • Pulmonary edema • Pulmonary fibrosis • Radiation hepatitis • Radiation induced disease, acute • Radio Embolization 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. **CAUTION:** Federal (USA) law restricts this device to sale by or on order of a physician. PI-992004-AA. **Note:** Dose to the liver does not exceed 150 Gy.

Simplicit90Y™ Personalized Dosimetry Software

Intended Use (US Only): Simplicit90Y™ is intended to be used by trained medical professionals for TheraSphere™ pre-treatment dosimetry planning and post-treatment dosimetry evaluation following Y90 treatment. Simplicit90Y is a medical image and information management system that is intended to receive, transmit, store, retrieve, display and process digital medical images, as well as create, display and print reports from those images. The medical modalities of these medical imaging systems include, but are not limited to, CT, MRI, SPECT and PET. Simplicit90Y provides the user with the means to display, register and fuse medical images from multiple modalities. Simplicit90Y provides tools to create, transform, and modify contours for the user to define objects in medical image volumes for use in TheraSphere pre-treatment dosimetry planning and for post-treatment dosimetry. The objects include, but are not limited to, tumors and normal tissues. For post-Yttrium-90 (Y90) treatment, Simplicit90Y should only be used for the retrospective determination of dose and should not be used to prospectively calculate dose or for the case where there is a need for retreatment using Y90 microspheres.

Indication for Use (US Only): Simplicit90Y is a standalone software device that is used by trained medical professionals as a tool to aid in evaluation and information management of digital medical images. Simplicit90Y supports the reading, rendering and display of a range of DICOM compliant imaging and related formats including but not limited to CT, PT, NM, SPECT, MR, SC, RTSS. Simplicit90Y enables the saving of sessions in a proprietary format as well as the export of formats including CSV and PDF files. Simplicit90Y is indicated, as an accessory to TheraSphere, to provide pre-treatment dosimetry planning support including Lung Shunt Fraction estimation (based on planar scintigraphy) and liver single-compartment MIRD schema dosimetry, in accordance with TheraSphere labelling. Simplicit90Y provides tools to create, transform, and modify contours/Regions of Interest for calculation of Lung Shunt Fraction and Perfused Volume. Simplicit90Y includes features to aid in TheraSphere dose vial selection, dose vial ordering and creation of customizable reports. Simplicit90Y is indicated for post-treatment dosimetry and evaluation following Yttrium-90 (Y-90) microsphere treatment. Simplicit90Y provides tools to create, transform, and modify contours/Regions of Interest for the user to define objects in medical image volumes to support TheraSphere post-Y-90 treatment calculation and evaluation. The objects include, but are not limited to, tumors and normal tissues, and liver volumes. Simplicit90Y is indicated for registration, fusion display and review of medical images allowing medical professionals to incorporate images, such as CT, MRI, PET, CBCT and SPECT in TheraSphere Yttrium-90 (Y-90) microspheres pre-treatment planning and post-Y-90 treatment evaluation For post-Yttrium-90 (Y-90) treatment, Simplicit90Y should only be used for the retrospective determination of dose and should not be used to prospectively calculate dose or for the case where there is a need for retreatment using Y-90 microspheres. PI-994110-AA

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