Summary of Safety and Clinical Performance

for

LifePearl™ Microspheres

SSCP22-0006 Rev C

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*Annual entries must be included. An entry stating such must be added if a revision is not required.

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1 SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions For Use (IFU) as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

1.1 Device Identification and General Information

Table 1.1 Device Identification and General Information

Device Names	
Device Trade Name	LifePearl Microspheres
EMDN Code	C01040200303- Embolization particles and microspheres
Medical Device Nomenclature (EMDN)	Embolic Beads
Device Class	Class III
Basic UDI-DI	08402732LIFEPEARL3D
Year when first certificate (CE) was issued for the device	2015
Legal Manufacturer	
Name & Address	MicroVention, Inc. 35 Enterprise Aliso Viejo, California, 92656 USA
Manufacturer SRN	US-MF-000016658
Authorized Representative	
Name & Address	MicroVention Europe SARL 30 bis, rue du Vieil Abreuvoir 78100 Saint-Germain-en-Laye, France
Authorized Representative SRN	FR-AR-000004448
Notified Body	
Name & Address	DQS Medizinprodukte GmbH August-Schanz-Straße 21 D-60433 Frankfurt am Main Germany
Notified Body Identification Number	0297

1.2 Intended Purpose of the Device

Table 1.2 Intended Use

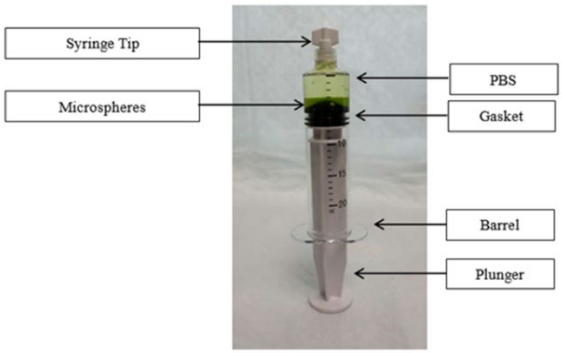
Intended Purpose	
Intended Purpose	LifePearl Microspheres is a preformed, compressible, precisely calibrated, spherical embolic agent consisting of a biocompatible hydrogel and capable of loading and releasing chemotherapeutic agents in a controlled manner.
Indications for Use	LifePearl Microspheres are indicated for embolization of blood vessels supplying primary hypervascular tumors or metastases in the liver. Note: LifePearl Microspheres can be loaded with chemotherapeutic drugs. When used for drug loading, drug loading should be done under a physician's direction, choice, and responsibility, based on type and dose of drug most beneficial to the patient.
Target Population	LifePearl Microspheres are intended for patients who have hypervascular primary hepatocellular carcinomas and/or metastases from other cancers to the liver. The microspheres, with pre-loaded chemotherapeutic agents for ancillary treatment of the tumors, serve to embolize the blood vessels supplying these hypervascular neoplasms. Percutaneous transcatheter embolization is a widely practiced method of therapeutic vascular occlusion that has been successfully applied in virtually every vascular territory to address hemorrhage, occlude congenital and acquired vascular abnormalities, palliate neoplasms, and infarct tissue. With accumulated experience and progression in the design of embolization agents and delivery devices, embolization became treatment of choice for many vascular abnormalities. Embolization can be performed either as a definitive treatment or as an adjunct to subsequent surgical management. Safe and effective application of embolic therapy requires high-level catheter skills, familiarity with the embolic agent being used, and knowledge of any agent- specific delivery considerations. Percutaneous transcatheter embolization is defined as the intravascular deposition of a device or agent (solid or liquid) to produce intentional vessel occlusion. Embolic vascular occlusion may be performed at any level from large arteries or veins to capillary beds, and it may be temporary or permanent in nature. Depending on the indication the degree of embolization may require partial or complete occlusion of vascular territory. The embolization may be a procedure in and of itself or a component of an intervention for regional drug, gene, radiation, or other biologic therapy.

Contraindications and/or Limitations	- Targeted embolization of blood vessels belonging to the central vascular system (arteriae pulmonles, aorta ascendens, arcus aorta, aorta descendens to the burficatio aortae, arteriae coronariae, arteria carotis communis, arteria carotis externa, arteria carotis interna, arteriae cerebrales, truncus brachiocephalicus, venae cordis, venae pulmonales, vena cava superior, vena cava inferior) - Patients intolerant to vascular occlusion procedures. - Vascular anatomy or blood flow that precludes catheter placement or embolic agent injection. - Presence or likely onset of vasospasm or hemorrhage. - Presence of severe atheromatous disease. - Presence of feeding arteries smaller than distal branches from which they emerge. - Presence of collateral vessel pathways potentially endangering normal territories during embolisation. - Presence of arteries supplying the lesion not large enough to accept LifePearl Microspheres. - Vascular resistance peripheral to the feeding arteries precluding passage of LifePearl Microspheres into the lesion. - Patient is pregnant - Patient has known allergies to radio-opaque contrast agent, drugs and their additives.- - Do not use LifePearl Microspheres in the following applications: i. Embolisation of non-malignant tumours. ii. Embolisation of large diameter arteriovenous shunts (i.e. where the blood does not pass through the arterial/capillary/venous transition but directly from artery to vein). Any vasculature where LifePearl Microspheres could pass directly into non-target territories.

1.3 Device Description

Table 1.3 Device Description

Device Description	
Description of the Device	LifePearl Microspheres is a preformed, compressible, precisely calibrated, spherical embolic agent consisting of a biocompatible hydrogel and capable of loading and releasing chemotherapeutic agents in a controlled manner. See **Figure 1** for product picture. LifePearl has a range of microspheres of 100 to 400 µm in diameter, supported by three different product codes: 8LP2S100 (100 ± 25 µm), 8LP2S200 (200 ± 50 µm) and 8LPS400 (400 ± 50 µm). LifePearl Microspheres is produced from a biocompatible hydrogel comprising polyethylene glycol (PEG) 10k diacrylamide that has been modified with sulphonate groups for the controlled loading and delivery of chemotherapy drugs. The polyethylene glycol (PEG) 10k diacrylamide is a derivatized, straight chain polyethylene glycol, average molecular weight 10,000. The two

	hydroxyl units on either end are replaced with acrylamide moieties, making it more amenable to chain polymerization. 3-Sulfopropyl acrylate and its derivatives are commonly used in drug loading polymers. The sulfopropyl monomer is commonly polymerized with another monomer to create a hydrogel crosslinked polymer. The drug loadable microspheres, DC Beads, was approved for use in humans is one such application. LifePearl Microspheres are tinted with green color using a reactive dye. This is to avoid the interference with the color of the drug and to allow visualization during re-constitution by the pharmacist. It is packaged in a 20 ml graduated syringe (from Merit Medical, CE – marked) pre-filled with 2 ml of the designated sphere size suspended in a non-pyrogenic, sterile transport solution of 4 ml phosphate buffered saline (PBS). The filled syringe is packaged in a sealed tray with a peel-away Tyvek® lid and sterilized in its packaging using steam sterilization. Each sealed tray is labeled and together with the Instructions for Use (IFU), drug loading instructions, patient implant card and information leaflet are packed inside a chipboard box unit. The product labels for the device are color coded based on the diameter of the microspheres: 8LP2S100 (black), 8LP2S200 (yellow) and 8LPS400 (blue). The labeled shelf life of the device is 3 years. **Figure 1: LifePearl Microspheres Diagram**  **LifePearl Microspheres in Syringe**
Design Characteristics of the Device	The microspheres themselves function as a physical impediment to the blood flow feeding the primary hepatic tumor or metastasis, by lodging in the vasculature of the treated blood vessels. The microspheres can be loaded with chemotherapeutic agents that serve as therapy against continued growth of the neoplasm. Once a delivery catheter is chosen based on the size of the target vessel, the delivery catheter is introduced into the target vessel according to the standard interventional techniques. LifePearl Microspheres is slowly injected into the delivery catheter while observing the contrast flow rate under fluoroscopic visualization. Upon completion of the treatment, the catheter is removed and any unused LifePearl Microspheres is discarded.
Previous Generations or Variants, if applicable	N/A

Single use – sterilization method	The product is provided sterile (E-beam sterilization) and is for single use only.
Description of Accessories	Not applicable, as no accessories are provided with the device.
Description of other Devices or Products intended to be used in combination	LifePearl Microspheres can be loaded with chemotherapeutic drugs. When used for drug loading, drug loading should be done under a physician's direction, choice and responsibility, based on type and dose of drug most beneficial to the patient.

1.4 Risks and Warnings

Vascular Embolisation is a high-risk procedure. The procedure should be performed by physicians trained in vascular embolisation procedures. Complications can occur at any time during or after the procedure and may include, but not limited to

- Undesirable reflux or passage of LifePearl Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
- Non-target embolization.
- Pulmonary embolization.
- Ischemia at an undesirable location.
- Capillary bed saturation and tissue damage.
- Ischemic stroke or ischemic infarction.
- Vessel or lesion rupture and hemorrhage.
- Neurological deficits including cranial nerve palsies.
- Vasospasm.
- Death.
- Recanalization.
- Foreign body reactions necessitating medical intervention.
- Infection necessitating medical intervention.
- Clot formation at the tip of the catheter and subsequent dislodgement.
- Hematoma, or bruising, at the incision site for arterial access.
- Arterial aneurysm at the incision site for arterial access.
- Deep vein thrombosis or clotting of a deep vein in a patient's leg.
- Thrombosis of the artery at the incision site for arterial access.
- Allergic reaction
- Risks of radiation from angiography and fluoroscopy used to visualize the blood vessels during embolization, which may include radiation burn and risks to future fertility.
- DO NOT USE LifePearl Microspheres in conjunction with embolization devices based on organic solvents such as ethyl alcohol and dimethyl sulfoxide (DMSO) at the same embolization site.

1.4.1 Residual Risks and Undesirable Effects

Hazards associated with the use of the LifePearl Microspheres are assessed and risks of the resulting harms are minimized through the use of risk mitigation/control measures. All known foreseeable risks have been evaluated and mitigated.

1.4.2 Warnings and Precautions

The warnings / precautions for LifePearl Microspheres are

- Undesirable reflux or passage of LifePearl Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
- Non-target embolization.
- Pulmonary embolization.
- Ischemia at an undesirable location.
- Capillary bed saturation and tissue damage.
- Ischemic stroke or ischemic infarction.
- Vessel or lesion rupture and haemorrhage.
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- Risks of radiation from angiography and fluoroscopy used to visualize the blood vessels during embolization, which may include radiation burn and risks to future fertility.
- DO NOT USE LifePearl Microspheres in conjunction with embolization devices based on organic solvents such as ethyl alcohol and dimethyl sulfoxide (DMSO) at the same embolization site.

1.4.3 Potential Complications / Adverse Effects

The potential complications / adverse effects for LifePearl Microspheres are

- Undesirable reflux or passage of LifePearl microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
- Non-target embolization.
- Pulmonary embolization.
- Ischemia at an undesirable location.
- Capillary bed saturation and tissue damage.
- Ischemic stroke or ischemic infarction.
- Vessel or lesion rupture and haemorrhage.
- Neurological deficits including cranial nerve palsies.
- Vasospasm.
- Death.
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- Risks of radiation from angiography and fluoroscopy used to visualize the blood vessels during embolization, which may include radiation burn and risks to future fertility.
- DO NOT USE LifePearl Microspheres in conjunction with embolization devices based on organic solvents such as ethyl alcohol and dimethyl sulfoxide (DMSO) at the same embolization site.

1.4.4 Other Aspects of Safety

There are no Field Actions or Recalls for LifePearl Microspheres.

1.5 Summary of the Clinical Evaluation and PMCF

1.5.1 Equivalent Device Clinical Data

Equivalence was not claimed for LifePearl Microspheres,

1.5.2 Pre-CE-Mark Clinical Data

There were no pre-market studies conducted for LifePearl Microspheres.

1.5.3 Clinical Data

Clinical evidence was identified, collected and appraised from post-market studies and registries, published peer reviewed literature, and the company's post-market surveillance data.

There were eight completed post-market clinical studies and registries identified that are directly sponsored or funded by research grant from Terumo including total 681 patients for the LifePearl Microspheres for using the LifePearl Microspheres for embolization of blood vessels supplying primary-hypervascular tumors or metastases in the liver and loading chemotherapeutic drugs. There is also one ongoing post-market study (LifePearl-IRI-GEMCAD study - NCT04595266) including 48 participants; this is an investigator-initiated study funded by a research grant from Terumo, and the study is expected to be completed in 2025. Of the 681 patients identified from the completed post-market clinical studies, some of these patients were also identified from the peer reviewed published literature by systematic literature search and review (refer to **Section 14.5**).

The Clinical Evaluation for LifePearl Microspheres investigated relevant clinical data from the scientific literature, investigator-sponsored clinical studies, and post-market surveillance data for the device. A total of 17 published articles including 7 retrospective studies, 9 prospective studies, and one pooled analysis from 3 retrospective registries and 2 prospective registries for LifePearl Microspheres were included in the evaluation including 1,664 patients (Aliberti et al., 2016, Aliberti et al., 2017, de Baere et al., 2020, Gjoreski et al., 2021, Gjoreski et al., 2019, Helmberger et al., 2022, Korsic et al., 2022, Lucatelli et al., 2019, Lucatelli et al., 2022, Malagari et al., 2022, Maleux et al., 2020, Mauri et al., 2022, Pereira et al., 2021, Tovar-Felice, 2021, Veloso Gomes et al., 2023, Veloso Gomes et al., 2018, Arnold et al., 2025). The literature search results demonstrate safe and effective use of the LifePearl™ Microspheres for embolization of blood vessels supplying primary-hypervascular tumors or metastases in the liver and loading chemotherapeutic drugs.

Post-market surveillance data show the use of LifePearl Microspheres in 24,189 cases from 01 01 September 2020 to 31 August 2024 with no reports of complaint that resulted in patient death; MicroVention received 24 product complaints concerning LifePearl Microspheres, resulting in a complaint rate of 0.099%. Of the 24 complaints received by MicroVention for the evaluation period of 01 September 2020 to 31 August 2024 regarding the LifePearl™ Microspheres,two events were deemed reportable to EU authorities resulting in a reportable complaint rate of 0.0083%.

Clinical risks of the use of the LifePearl Microspheres are consistent with the state of the art in medicine for microspheres, showing low rates of adverse events and low rates of complaints failure across a number of published studies with a large cumulative patient population and substantial post-market surveillance data.

There were no systematic misuses or off-label uses of the subject device identified in this report.

1.5.4 Clinical Performance and Safety

The clinical data from 8 completed post-market clinical studies and registries included 681 patients for using LifePearl Microspheres, demonstrating clinical risks and benefits with safety and performance outcomes. All studies showed the clinical use of LifePearl Microspheres for embolization of blood vessels supplying primary-hypervascular tumors or metastases in the liver and loading chemotherapeutic drugs. Of the 681 patients identified from the completed post-market clinical studies, some of these patients were also identified from the peer reviewed published literature by the systematic literature search. A summary of the safety and performance outcomes from the post-market studies and registries are shown below(**Table 1.4** and **Table 1.5**).

Table 1.4: Safety Outcomes - Post-Market Clinical Investigations

Completed Study	#Patients	Safety
LifePearl-Iri PK Study (NCT02547480)	15	• 14.3% (2/14) mortality rate - One death (7.1%) occurred in a patient with necrotizing pancreatitis, possibly related to TACE, but unlikely to the device. • 21.4% (3/14) Serious Adverse Events (SAE). 4 SAEs were noted, not related or unlikely related to the device: ▪ 1 SAE (respiratory failure Grade 3) in 100mg ▪ 3 SAE (constipation Grade 1, necrotizing pancreatitis Grade 5, and ischemic cholecystitis Grade 2) in 200mg dose group • 28.6% (4/14) grade ≥ 3 Adverse Events (AE)
LifePearl-Doxo PK Study (NCT02548780)	25	• No 30-day mortality (0%) after the first procedure • 4% grade 4 AE related to intrahepatic tumor rupture after the first procedure • Grade 3 AE including unexplained intra-abdominal hemorrhage after the first procedure, followed by ▪ Acute kidney failure in one patient (4%) ▪ Abdominal pain in one patient (4%) ▪ Nausea in one patient (4%) ▪ Aspartate aminotransferase increase in one patient (4%) • Grade 3 AEs after the second procedure including ▪ Abdominal pain in 4 patients (19%) ▪ Nausea in one patient (4.7%) *No device deficiencies or device failures, nor 30-day mortality were observed in the study
PARIS Registry (NCT03053596)	97	• Overall 73.2% (71/97) AE ▪ 13.4% (13/97) grade ≥ 3 AE related to the LifePearl Microspheres • 1.0% (1/97) mortality due to heart failure despite successful TACE procedure • 15.5% hepatotoxicity
Spanish Registry	50	• The clinical outcomes of 50 patients in the Spanish Registry are published (Tovar-Felice, 2021)
EMBOBEVA Study (NCT03732235)	40	There are two groups, in which one group received LifePearl Microspheres alone and the other group received LifePearl Microsperes with bevacizumab. • No complications (0%) observed during TACE in both groups

		• No thromboembolic effects or bleeding (0%) observed • The most frequently observed TACE-related adverse events were ▪ Pain (grade 2) in 24 patients (32%), which resolved in 2 days ▪ Elevated transaminase (grade 2-3) in 52 patients (68%) ▪ Most TACE-related adverse events were correlated with postembolization syndrome • Bevacizumab-related AEs are: ▪ Proteinuria (grade 2) in 12 patients (32%) ▪ Increased blood pressure (grade 2) in 10 patients (26%) ▪ Skin rash (grade 2) in 20 patients (53%)
The Single-center Retrospective Analysis	302	• The clinical outcomes of 302 patients from this registry are published (Veloso Gomes et al., 2018).
CIRSE Registry (NCT03086096)	152	• The clinical outcomes of 152 patients from this registry are published (Arnold et al., 2025, Helmberger et al., 2022)

Table 1.5: Performance Outcomes – Post-Market Clinical Investigations

Completed Study	#Patients	Performance
LifePearl-Iri PK Study (NCT02547480)	15	• 93% technical success • 70% Disease Control (DC) rate with 100mg irinotecan and 82% DC rate with 200mg irinotecan
LifePearl-Doxo PK Study (NCT02548780)	25	• 96% (24/25) technical success (achievement of stasis) • 81% best overall response rate • 90% DC rate at best • CR of 22%, 60%, and 43% at 3 months follow-up in the ≤75, 76–100, and 101–150 mg subgroups, respectively • 60% CR at 6 months in the total population • 52% CR, 29% PR, 10% SD, and 10% PD at best tumor response • Median 27.2 months Overall Survival (OS) time • Median 9.8 months Progression-Free Survival (PFS) time
PARIS Registry (NCT03053596)	97	• 81% OS at 1 year and 66% OS at 2-year follow-up • Median 10.6 months PFS time • Median 16.7 months TTUP (time to TACE untreatable progression) • 80.8% ORR • 98.9% DC
Spanish Registry	50	• The clinical outcomes of 50 patients in the Spanish Registry are published (Tovar-Felice, 2021).
EMBOBEVA Study (NCT03732235)	40	There are two groups, in which one group received LifePearl Microspheres alone and the other group received LifePearl Microspheres with bevacizumab. • OS and PFS did not differ significantly between TACE-B and TACE groups ▪ Median OS time (TACE-B) was 18 months ▪ Median OS time (TACE) was 15.8 months ▪ Median PFS time (TACE-B) was 13 months ▪ Median PFS time (TACE) was 11 months • The disease control rate at 1 and 3 months was significantly higher in the TACE-B group (100%) than in the TACE group (84%) • Patients with KRAS WT had significantly better tumor response (100% at 3 months and 91% at 6 months) than patients with KRAS mutation (96% at 3 months and 76% at 6 months) after TACE-B

The Single-center Retrospective Analysis	302	• The clinical outcomes of 302 patients from this registry are published (Veloso Gomes et al., 2018).
CIRSE Registry (NCT03086096)	152	• The clinical outcomes of 152 patients from this registry are published (Helmberger et al., 2022, Arnold et al., 2025).

The clinical data analyzed from the post-market clinical studies and registries are provided below. It is important to note that most TACE-related adverse events (grade 2 or 3) were correlated with postembolization syndrome due to chemotherapies.

- The post-market clinical studies report safety outcomes such as:
  - Grade 2 AE in 32-68%
  - Grade $\geq$ 3 AE in 4%-28.6% of the patients
    - Acute kidney failure, abdominal pain, nausea, and elevated aspartate aminotransferase
  - Grade 4 AE in 4% of the patients including intrahepatic tumor rupture
  - SAE in 21.4% of the patients
  - Death in 0%-14.3% of the patients
- The post-market clinical studies report performance outcomes such as:
  - Technical success in 93%-96% of the patients
  - Median OS time of 14.5 months-27.2 months
  - Median OS of 55-81% at 1-year
  - Median OS of 66% at 2-year
  - Median PFS time of 4.9 months-13 months
  - Median TTUP (Time to TACE Untreatable progression) of 16.7 months
  - ORR of 80.8%-81%
  - CR of 22%-60% at follow-up
  - PR of 29% at follow-up
  - SD of 10% at follow-up
  - PD of 10% at follow-up
  - DC rate of 70%-100%

The clinical data from the published literature included a total of 17 published studies, which are from seven retrospective studies, nine prospective studies, and one pooled analysis from three retrospective registries and two prospective registries for LifePearl Microspheres; the included published literature identified 1,664 patients demonstrating clinical risks and benefits with safety and performance outcomes. All studies demonstrated the clinical use of LifePearl Microspheres for embolization of blood vessels supplying primary-hypervascular tumors or metastases in the liver and loading chemotherapeutic drugs.(Aliberti et al., 2016, Aliberti et al., 2017, de Baere et al., 2020, Gjoreski et al., 2021, Gjoreski et al., 2019, Helmberger et al., 2022, Korsic et al., 2022, Lucatelli et al., 2019, Lucatelli et al., 2022, Malagari et al., 2022, Maleux et al., 2020, Mauri et al., 2022, Pereira et al., 2021, Tovar-Felice, 2021, Veloso Gomes et al., 2023, Veloso Gomes et al., 2018, Arnold et al., 2025) A summary of the safety and performance outcomes from the published literature are shown below. (**Table 1.6** and **Table 1.7**)

Table 1.6: Safety Outcomes of LifePearl™ Microspheres – Published Literature

Safety Outcome	Quantified Range
Postembolization Syndrome • Not limited to nausea and/or vomiting, alopecia, fever, fatigue, elevated temperature and diarrhea, etc	• 9 studies reporting post-embolization syndrome in 0.6%-52.6% of patients(Korsic et al., 2022, Lucatelli et al., 2022, G. Tovar-Felice, 2021, Aliberti et al., 2017, Aliberti et al., 2016, Veloso Gomes et al., 2018, Helmberger et al., 2022, Malagari et al., 2022, Veloso Gomes et al., 2023)
Anorexia	• 1 study reporting anorexia in 4% of the patients (Malagari et al., 2022)
Asthenia	• 1 study reporting asthenia in 4% of the patients (Malagari et al., 2022)
Pain	• 6 studies reporting postprocedural adverse events including pain in 8-57% of patients during follow-up (Gjoreski et al., 2021, Mauri et al., 2022, Pereira et al., 2021, Aliberti et al., 2017, Aliberti et al., 2016, Helmberger et al., 2022, Malagari et al., 2022)
Liver Abscess	• 3 studies reporting liver abscess in 1.7%-5% of patients during follow-up (Lucatelli et al., 2022, Pereira et al., 2021, Veloso Gomes et al., 2018)
Sepsis	• 1 study reporting sepsis in 2% of patients (Pereira et al., 2021)
Hepatic Decompensation/Failure	• 2 studies reporting hepatic decompensation/failure in 0.6%-2% of patients(Pereira et al., 2021, Helmberger et al., 2022)
Hepatic Encephalopathy	• 1 study reporting hepatic encephalopathy in 4% of patients (Malagari et al., 2022)
Cholecystitis	• 2 studies reporting cholecystitis in 1.3%-2% of patients (Pereira et al., 2021, Helmberger et al., 2022)
Infection	• 1 study reporting infection in 4% of patients (Pereira et al., 2021)
Hepatotoxicity	• 1 study reporting hepatotoxicity in 15.5% of the patients (de Baere et al., 2020)
Increased transaminase level	• 1 study reporting increased transaminase level in 17% of the patients (Aliberti et al., 2017)
Gastritis	• 1 study reporting gastritis in 15% of the patients (Aliberti et al., 2016)
Hematoma	• 1 study reporting hematoma in 1% of the patients (Veloso Gomes et al., 2018)
Vertigo	• 1 study reporting vertigo in 1.3% of the patients (Helmberger et al., 2022)
Neutropenia	• 1 study reporting neutropenia in 1.9% of the patients (Helmberger et al., 2022)
Thrombocytopenia	• 1 study reporting thrombocytopenia in 1.3% of the patients (Helmberger et al., 2022)
Acute Kidney Failure (Grade 3)	• 1 study reporting acute kidney failure (grade 3) in 4% of patients (Malagari et al., 2022)
Tumor Rupture & Bleeding	• 1 study reporting tumor rupture and bleeding (grade 4) in 4% of patients (Malagari et al., 2022)
SAE (Serious Adverse Event) • **Femoral Pseudoaneurysm** • **Ascitic Decompensation** • **Cholecystitis**	• 1 study reporting SAE in 8% of patients including femoral pseudoaneurysm, ascitic decompensation, and cholecystitis (G. Tovar-Felice, 2021)
Death	• 1 study reporting 5% mortality rate due to liver abscess (Lucatelli et al., 2022)

Table 1.7: Performance Outcomes of LifePearl™ Microspheres – Published Literature

Performance Outcome	Quantified Range
Technical Success (Complete Stasis / Embolization or Complete Delivery of Dose)	• 5 studies with 88-100% technical success (e.g., complete embolization or complete delivery of dose) (Mauri et al., 2022, Pereira et al., 2021, G. Tovar-Felice, 2021, Maleux et al., 2020, Helmberger et al., 2022)
Overall Survival (OS %)	• 6 studies reporting 55%-93.5% OS rate at 12 months (Korsic et al., 2022, G. Tovar-Felice, 2021, de Baere et al., 2020, Veloso Gomes et al., 2018, Veloso Gomes et al., 2023, Arnold et al., 2025) • 1 study reporting 80.1% OS rate at 18 months(Veloso Gomes et al., 2023) • 4 studies reporting 53-75.8% OS rate at 24 months(Korsic et al., 2022, G. Tovar-Felice, 2021, de Baere et al., 2020, Veloso Gomes et al., 2023)
Overall Survival Time (months)	• 6 studies reporting median 14.5-50.8 months survival time (Gjoreski et al., 2021, Korsic et al., 2022, G. Tovar-Felice, 2021, Malagari et al., 2022, Veloso Gomes et al., 2023, Arnold et al., 2025)
Progression-Free Survival (PFS%)	• 2 studies reporting 55-65.9% progression-free survival (PFS) rate at 12-months (Veloso Gomes et al., 2018, Arnold et al., 2025)
Progression-Free Survival (PFS) Time (months)	• 2 studies reporting median 4.6-15.6 months progression-survival (PFS) time (Malagari et al., 2022, Veloso Gomes et al., 2023, Arnold et al., 2025)
Objective Response Rate (ORR%)	• 6 studies reporting 70-95% objective response rate at follow-up (Lucatelli et al., 2022, de Baere et al., 2020, Aliberti et al., 2016, Aliberti et al., 2017, Malagari et al., 2022, Veloso Gomes et al., 2023)
Complete Response (CR%)	• 7 studies reporting 43%-63.2% complete response rate at follow-up (Lucatelli et al., 2022, G. Tovar-Felice, 2021, Veloso Gomes et al., 2018, Aliberti et al., 2016, Aliberti et al., 2017, Malagari et al., 2022, Veloso Gomes et al., 2023)
Partial Response (PR%)	• 5 studies reporting 19%-37% partial response rate at follow-up (Veloso Gomes et al., 2018, Aliberti et al., 2016, Aliberti et al., 2017, Malagari et al., 2022, Veloso Gomes et al., 2023)
Stable Disease (SD%)	• 4 studies reporting 5.7%-29% stable disease rate at follow-up (Veloso Gomes et al., 2018, Aliberti et al., 2017, Malagari et al., 2022, Veloso Gomes et al., 2023)
Progressive Disease (PD%)	• 5 studies reporting 0%-10% progressive disease rate at follow-up (Lucatelli et al., 2022, Veloso Gomes et al., 2018, Aliberti et al., 2017, Malagari et al., 2022, Veloso Gomes et al., 2023)
Disease Control (DC%)	• 5 studies reporting 91%-100% disease control rate at follow-up (Lucatelli et al., 2022, G. Tovar-Felice, 2021, de Baere et al., 2020, Malagari et al., 2022, Veloso Gomes et al., 2023)

Overall, the clinical data from both post-market clinical investigations and published literature with 1,841 patients demonstrated acceptable clinical risks and benefits with reported safety and performance outcomes; all studies showed the clinical use of LifePearl Microspheres for embolization of blood vessels supplying primary-hypervascular tumors or metastases in the liver and loading chemotherapeutic drugs.

1.5.5 Post-Market Clinical Follow-up

One Post-Market Clinical Follow-up study for LifePearl Microspheres is currently enrolling patients. The LifePearl-IRI-GEMCAD Study (NCT04595266) will include 48 patients with colorectal cancer and exclusive liver metastases and is expected to be completed in 2025.

1.6 Possible Diagnostic or Therapeutic Alternatives

1.6.1 Treatment Options and Interventions

There have been significant advances in hepatocellular carcinoma (HCC) treatment over the past 10 years. The American Association for the Study of Liver Diseases (ASSLD) guidelines divide treatment options into curative and noncurative interventions. Curative treatment offers the chance of long-term response and improved the survival and non-curative treatment attempts to prolong survival by slowing tumor progression.

Examples of curative treatments include:

- Surgical Resection
- Liver Transplant
- Ablation therapy

Examples of noncurative treatments:

- Trans-arterial chemoembolization
- Trans-arterial radioembolization
- Stereotactic body radiation therapy
- Systemic chemotherapy

1.6.2 Available Technologies

BioPearl Microspheres are well-established medical devices with numerous types and styles available from a variety of manufacturers. Examples of microspheres similar to the BioPearl Microspheres are listed in Table 1.4.

Table 1.8 Similar Devices

Device	Manufacturer	Intended Purpose
DC Bead™ Microspheres	Boston Scientific	DC Bead is intended to be loaded with: Doxorubicin for the purpose of • Embolization of vessels supplying malignant hypervascular tumors

		• Delivery of local, controlled sustained dose of doxorubicin to the tumors Irinotecan for the purpose of • Embolization of vessels supplying malignant colorectal cancer metastasized to the liver (mCRC) Delivery of a local controlled sustained dose of irinotecan to the mCRC.
HepaShere™ Microspheres	Merit Medical	HepaSphere Microspheres are indicated for use in embolization of blood vessels with or without delivery of doxorubicin HCl for therapeutic or preoperative purposes in the following procedures: • Embolization of hepatocellular carcinoma • Embolization of metastases to the liver. HepaSphere Microspheres loaded with irinotecan are indicated for use in: Embolization of metastatic colorectal cancer (mCRC) to the liver.

1.7 Suggested Profile and Training for Users

Vascular Embolization is a high-risk procedure. The procedure should be performed by physicians trained in vascular embolization procedures.

1.8 Reference to any Harmonized Standards and CS

Standard Number	Edition	Standard Title (equivalent edition)
EN ISO 13485	2016/A11:2021	Medical devices - Quality management systems - Requirements for regulatory purposes (ISO 13485:2016)
EN ISO 14971	2019/A11:2021	Medical devices - Application of risk management to medical devices (ISO 14971:2019)
EN ICE 60812	2018	Failure modes and effects analysis (FMEA and FMECA) (IEC 60812:2018)
EN 62366-1	2015/A1:2020	Medical devices - Part 1: Application of usability engineering to medical devices (IEC 62366-1:2015/A1:2020)
EN ISO 14155	2020	Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2020)
ISO/TR 20416	2020	Medical devices - Post-market surveillance for manufacturers

Standard Number	Edition	Standard Title (equivalent edition)
EN ISO 15223-1	2021	Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements (ISO 15223-1:2021)
EN ISO 20417	2021	Medical devices - Information to be supplied by the manufacturer (ISO 20417:2021, Corrected version 2021-12)
EN ISO 11607-1	2020/A1:2023	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2019/Amd 1:2023)
EN ISO 11607-2	2020/A1:2023	Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes (ISO 11607-2:2019/Amd 1:2023)
ISTA 3A	2018	Packaged-Products for Parcel Delivery System Shipment 70 kg (150 lbs) or Less
ASTM D4169	2023e1	Standard Practice for Performance Testing of Shipping Containers and Systems
ASTM F88	2023	Standard Test Method for Seal Strength of Flexible Barrier Materials
ASTM F1886	2016	Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection
ASTM F1929	2023	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration
ASTM F2096	2011R2019	Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)
ASTM F1980	2016	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
EN ISO 10993-1	2020	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2018, including corrected version 2018-10)
EN ISO 10993-3	2014	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity (ISO 10993-3:2014)
EN ISO 10993-4	2017	Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood (ISO 10993-4:2017)
EN ISO 10993-5	2009	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity (ISO 10993-5:2009)
EN ISO 10993-6	2016	Biological evaluation of medical devices - Part 6: Tests for local effects after implantation (ISO 10993-6:2016)
EN ISO 10993-10	2023	Biological evaluation of medical devices - Part 10: Tests for skin sensitization (ISO 10993-10:2021)

Standard Number	Edition	Standard Title (equivalent edition)
EN ISO 10993-11	2018	Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO 10993-11:2017)
EN ISO 10993-12	2021	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (ISO 10993-12:2021)
EN ISO 10993-17	2023	Biological evaluation of medical devices - Part 17: Toxicological risk assessment of medical device constituents (ISO 10993-17:2023)
EN ISO 10993-23	2021	Biological evaluation of medical devices - Part 23: Tests for irritation (ISO 10993-23:2021)
EN ISO 14644-1	2015	Cleanrooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration (ISO 14644-1:2015)
EN ISO 14644-2	2015	Cleanrooms and associated controlled environments - Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration (ISO 14644-2:2015)
ANSI/AAMI ST72	2019	Bacterial endotoxins – Test methods, routine monitoring, and alternatives to batch testing
EN 556-1	2001/AC:2006	Sterilization of medical devices – Requirements for medical devices to be designated ‘STERILE’ – Part 1: Requirements for terminally sterilized medical devices
EN ISO 11737-1	2018/A1:2021	Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products (ISO 11737-1:2018/Amd 1:2021)
EN ISO 11737-2	2020	Sterilization of health care products - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process (ISO 11737-2:2019)
ISO 11737-3	2023	Sterilization of health care products - Microbiological methods - Part 3: Bacterial Endotoxin testing
EN ISO 11138-1	2017	Sterilization of health care products - Biological indicators - Part 1: General requirements (ISO 11138-1:2017)
EN ISO 17665-1	2006	Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices (ISO 17665-1:2006)

Standard Number	Edition	Standard Title (equivalent edition)
EN ISO 17665 (supersedes EN ISO 17665-1)	2024	Sterilization of health care products - Moist heat - Requirements for the development, validation and routine control of a sterilization process for medical devices (ISO 17665:2024)
EN ISO 80369-7	2021	Small-bore connectors for liquids and gases in healthcare applications - Part 7: Connectors for intravascular or hypodermic applications (ISO 80369-7:2021)
EN ISO 14630	2012	Non-active surgical implants - General requirements (ISO 14630:2012)
ASTM F2052	2021	Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment
ASTM F2119	2007R2013	Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants
ASTM F2182	2019e2	Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging
ASTM F2213	2017	Standard test method for measurement of magnetically induced torque on passive implants in the magnetic resonance
ASTM F2503	2023e1	Standard practice for marketing medical devices and other items for safety in the magnetic resonance environment

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