Summary of Safety and Clinical Performance (SSCP)

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 HepaSphere Microspheres.

The SSCP is not intended to replace the instructions for use as the main document to ensure the safe use of the HepaSphere Microspheres, nor to provide diagnostic or therapeutic suggestions to intended users or patients.

The English version of this SSCP document (SSCP0002) has been validated by the notified body. The following information is intended for users/healthcare professionals. A more general information summary is provided for patients and lay persons.

1.0 Device identification and general information

HepaSphere Microspheres were first CE-marked by Biosphere Medical in 2004 for the embolization of hepatocellular carcinoma and metastases to the liver. Chemoembolization with HepaSphere Microspheres loaded with doxorubicin for hepatocellular carcinoma and metastases to the liver received CE-mark in 2007. More recently, HepaSphere Microspheres loaded with irinotecan has been approved for embolization of metastatic colorectal cancer (mCRC) to the liver (CE-mark in 2015).

1.1 Device trade name:

The device trade name is HepaSphere® Microspheres, and the model numbers covered by this SSCP are presented in Table 1.

Table 1. Devices Included in this Summary of Safety and Clinical Performance

Nominal dry size (µm)	Size after Reconstitution (µm)	Colour code	Reference code by weight	
			25 mg vial	50 mg vial
20-40*	80-160	Grey*	V125HS*	V150HS*
30-60	120-240	Orange	V225HS	V250HS
50-100	200-400	Yellow	V325HS	V350HS
100-150	400-600	Blue	V525HS	V550HS
150-200	600-800	Red	V725HS	V750HS

*HepaSphere Q2 Microspheres is also a brand name of the 20-40µm size range

1.2 Manufacturer Information

The name and address of the manufacturer of the HepaSphere Microspheres are provided in Table 2.

Table 2. Manufacturer Information

Manufacturer Name	Address of Manufacturer
Biosphere Medical S.A.	Parc des Nations – Paris Nord II, 383 Rue de la Belle Etoile, 95700 Roissy en France, FRANCE

1.3 Manufacturer Single Registration Number (SRN)

The Single Registration Number for the manufacturer is included in Table 3 and Table 4.

1.4 Basic UDI-DI

The basic Unique Device Identifier (UDI) with Device Identification (DI) key is provided in

Table 3.

1.5 Medical Device Nomenclature Description / Text

The "Classificazione Nazionale dei Dispositivi medici" (CND)/European Medical Device Nomenclature (EMDN) code and descriptor for the subject device are listed in

Table 3.

1.6 Risk Class of Device

The EU device risk classifications for the HepaSphere Microspheres are listed in

Table 3.

Table 3. Device Identification Information

Device Name	EU Device Class	Product Number	Basic UDI-DI	Single Registration Number (SRN)	CND/EMDN Code	CND/EMDN Terms
HepaSphere Microspheres Q2 20-40 µm – 25 mg	III	V125HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres Q2 20-40 µm – 50 mg	III	V150HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres 20-40 µm – 25 mg	III	V125HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres 20-40 µm – 50 mg	III	V150HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres 30-60 µm – 25 mg	III	V225HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres	III	V250HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres

Device Name	EU Device Class	Product Number	Basic UDI-DI	Single Registration Number (SRN)	CND/EMDN Code	CND/EMDN Terms
30-60 µm – 50 mg						
HepaSphere Microspheres 50-100 µm – 25 mg	III	V325HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres 50-100 µm – 50 mg	III	V350HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres 100-150 µm – 25 mg	III	V525HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres 100-150 µm – 50 mg	III	V550HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres 150-200 µm – 25 mg	III	V725HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres
HepaSphere Microspheres 150-200 µm – 50 mg	III	V750HS	088445048755E9	FR-MF-000005250	C010402020303	EMBOLIZATION IMPLANTS AND SYSTEMS / Embolization Particles and Microspheres

1.7 Year of EU Market Introduction

The year that the HepaSphere Microspheres was first placed on the European Union market is presented in Table 4.

1.8 Authorised Representative (if applicable)

Non applicable.

1.9 Notified Body name and NB's Single Identification Number

The Notified Body (NB) involved in the conformity assessment of the HepaSphere Microspheres in accordance with Annex IX of the Medical Device Regulation 2017/745 of the European Union and responsible for validating the SSCP is listed in Table 4.

The NB Single Identification Number is listed in Table 4.

Table 4. Legal manufacturer and Notified Body Information

Device Name	Year Placed on EU Market	Legal Manufacturer		Notified Body	
		Name	SRN	Name	ID Number
HepaSphere Microspheres Q2 20-40 µm – 25 mg	2019	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres Q2 20-40 µm – 50 mg	2019	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 20-40 µm – 25 mg	2019	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 20-40 µm – 50 mg	2019	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 30-60 µm – 25 mg	2013	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 30-60 µm – 50 mg	2013	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 50-100 µm – 25 mg	2006	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 50-100 µm – 50 mg	2006	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 100-150 µm – 25 mg	2006	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 100-150 µm – 50 mg	2006	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 150-200 µm – 25 mg	2006	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459
HepaSphere Microspheres 150-200 µm – 50 mg	2006	Biosphere Medical S.A.	FR-MF-000005250	GMED	0459

2.0 Intended Use of the Device

2.1 Intended Purpose

HepaSphere Microspheres are designed for controlled, targeted embolization.

2.2 Indications

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.

2.3 Intended Patient Groups

The device HepaSphere Microspheres is intended for therapeutic or preoperative embolization for:

- Patients with hepatocellular carcinoma
- Patients with metastases to the liver
- Patients with metastatic colorectal cancer (mCRC) to the liver

Transarterial chemoembolization is indicated for patients with intermediate HCC (BCLC B disease) that are not suitable for ablation intervention in Child-Pugh A or B cirrhotic with performance status 0–1. Approximately 90% of HCCs are associated with a known underlying etiology, most frequently chronic viral hepatitis (B and C). The gender ratio is 70% of men for 30% of women with a mean age of 64 years old.

Metastases to the liver, including mCRC correspond to an advanced stage of primary tumors. The gender ratio is 70% of men for 30% of women with a mean age of 61 years old.

2.4 Contraindications:

<u>All indications</u>

- Patients intolerant to vascular occlusion procedures
- Vascular anatomy or blood flow precluding correct catheter placement or embolic injection
- Presence or suspicion of vasospasm
- Presence or likely onset of haemorrhage

- Presence of severe atheromatous disease
- Presence of collateral vessel pathways potentially endangering normal territories during embolization
- High flow arteriovenous shunts or fistulae with luminal diameter greater than the selected size of HepaSphere Microspheres
- Vascular resistance peripheral to the feeding arteries precluding passage of HepaSphere Microspheres into the lesion
- Do not use in pulmonary vasculature, coronary and central nervous system vasculature
- Known sensitivity to poly vinyl alcohol-co-sodium acrylate

3.0 Device Description

HepaSphere Microspheres are part of a family of embolic agents based on Merit Medical's proprietary technology. These spheres are designed for controlled, targeted embolisation.

HepaSphere Microspheres are made of an acrylic copolymer. They are biocompatible, hydrophilic, non-resorbable, expandable and conformable microspheres. HepaSphere Microspheres swell upon exposure to aqueous solutions. They can be loaded with doxorubicin HCl or irinotecan and are able to release the drug locally at the embolization site.

The microspheres are contained in a sterile, 10 ml vial, with a crimped cap, individually packaged in a sealed pouch. Contents: 25 mg or 50 mg of dry HepaSphere Microspheres per vial to be reconstituted before use. One (1) sealed unit packed is placed inside a carton box with one (1) IFU.

3.1 Materials/Substances in Contact with Patient Tissues and Operating principles

Only the acrylic copolymer (poly vinyl alcohol-co-sodium acrylate) microspheres (Figure 1) will be in contact with vessels of the patient.

The procedure of arterial embolization is similar for all arteries. Appropriately sized microspheres for target vessel occlusion are chosen by the trained interventional radiologist. The delivery procedure involves arterial access through an artery, using a guidewire and microcatheter under fluoroscopic guidance. Once the catheter tip is placed in the artery(ies) supplying the targeted tissue, HepaSphere Microspheres mixed with a non-ionic contrast agent are delivered in a controlled manner under visualization and mechanically occlude the feeding vessel(s) to interrupt artery blood flow to the targeted area.

HepaSphere Microspheres have properties of loading with chemotherapeutic agents. The loading of HepaSphere Microspheres with chemotherapeutic agents occurs by 2 mechanisms:

- passive absorption by swelling from its dry state in an aqueous solution of the drug
- ionic bonding between negatively charged carboxylate groups of HepaSphere Microspheres and positively charged amine groups such as Irinotecan.

HepaSphere Microspheres can occlude blood flow to the target tissue and deliver a local and sustained dose of chemotherapeutic agent directly to the tumor. HepaSphere Microspheres enables high drug concentration that is targeted and delivered directly to the tumor site, resulting in fewer drug-related adverse events.

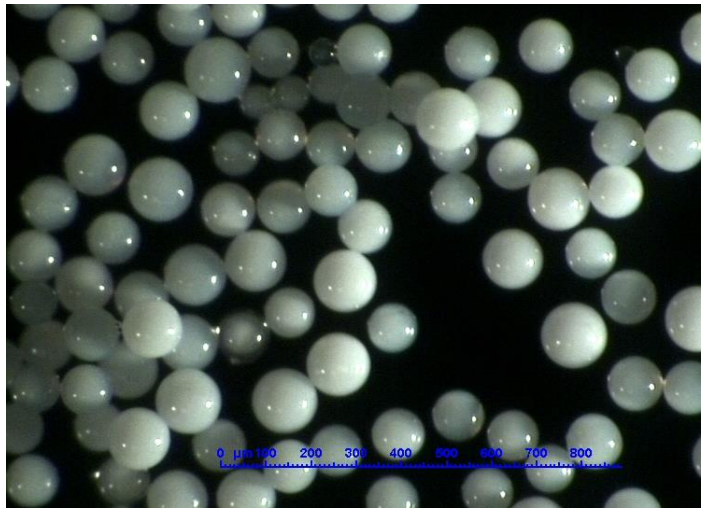

Figure 1. Picture of HepaSphere Microspheres

3.2 Previous Generations or Variants

There are no applicable prior device generations or variants.

3.3 Accessories, Devices and Product to be Used in Combination with HepaSphere Microspheres

HepaSphere Microspheres are compatible with the microcatheters listed in Table 5.

Table 5. HepaSphere Microspheres Catheter Compatibility

Dry Size Range (µm)	Size after reconstitution (µm)	Color Code	25 mg	50 mg	Minimum Catheter ID
20-40	80-160	Grey	V125HS	V150HS	0.020 in (0.51 mm)
30-60	120-240	Orange	V225HS	V250HS	0.021 in (0.53 mm)
50-100	200-400	Yellow	V325HS	V350HS	0.021 in (0.53 mm)
100-150	400-600	Blue	V525HS	V550HS	0.024 in (0.61 mm)
150-200	600-800	Red	V725HS	V750HS	0.027 in (0.63 mm)

Abbreviations: ID = inner diameter, in = inch, mg = milligram, mm = millimeter, µm = micrometer

Table 6 summarizes the accessories not supplied with the product but required for its use as defined in product IFU.

Table 6. Accessories not included with the device but necessary for use

Procedure		Component	Comment
Preparation for embolization	Without drug (bland)	Saline solution	Reconstitution medium: The microspheres are prepared with a mixture of 50% saline solution and 50% non-ionic contrast agent (for visualization under fluoroscopy).
		Contrast medium	
		10-mL syringe and 20-gauge diameter or larger needle	To inject the reconstitution medium into the HepaSphere vial.
		30-mL syringe and 20-gauge or larger needle	Aspirate the contents of the vial into a 30-mL syringe.
	With doxorubicin	Up to 75mg doxorubicin 20-mL saline solution when doxorubicin in powder 2 x 30-mL syringe 1 x 20-gauge diameter or larger needle	To prepare the microspheres with doxorubicin.

Procedure		Component	Comment
	With irinotecan	100mg irinotecan 1 x syringe and 20-gauge or larger needle	To prepare the microspheres with irinotecan.
Delivery instructions		Injection syringe no larger than 3-mL (1-mL injection syringe recommended)	The microspheres are transferred into an injection syringe through a three-way stopcock.
		Three-way stopcock	
		Microcatheter	The microspheres are injected into the patient through a microcatheter.

Abbreviations: mg = milligram, mL = milliliter

4.0 Risks and Warnings

4.1 Residual Risks and Undesirable Effects

The potential complications/undesirable side effects related to the HepaSphere Microspheres device as identified in the Instructions For Use are summarized in Table 7.

Table 7. HepaSphere Microspheres: Potential Complications

Product Configuration	Potential Adverse Events
HepaSphere Microspheres HepaSphere Q2 Microspheres	Vascular embolization is a high-risk procedure. Complications may occur at any time during or after the procedure, and may include, but are not limited to, the following: • Post-embolization syndrome (such as nausea, vomiting, pain, fever) • Fatigue and loss of appetite • Hypertension • Liver disorders or failure (including liver enzyme anomalies and ascites) • Complications related to catheterization (e.g., haematoma at the site of entry, clot formation at the tip of the catheter and subsequent dislodgement, and nerve and/or circulatory injuries which may result in leg injury) • Vessel or lesion rupture and hemorrhage • Vasospasm

Product Configuration	Potential Adverse Events
	• Recanalisation • Allergic reaction to medications (e.g., analgesics) • Allergic reaction to non-ionic contrast media or embolic material • Undesirable reflux or passage of HepaSphere Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds, such as the internal carotid artery, pulmonary, or coronary circulation • Pulmonary embolism due to arteriovenous shunting • Pleural effusion • Ischemia at an undesired location, including ischemic stroke, ischemic infarction (including myocardial infarction), and tissue necrosis • Capillary bed occlusion and tissue damage (cholecystitis, cholangitis, pancreatitis) • Paralysis resulting from untargeted embolization or ischemic injury from adjacent tissue oedema • Blindness, hearing loss, and loss of smell • Foreign body reactions necessitating medical intervention • Infection necessitating medical intervention (including liver abscess) • Death

4.2 Warnings and Precautions

Table 8. HepaSphere Microspheres: Warning and Precautions

Product Configuration	Labeling
HepaSphere Microspheres HepaSphere Q2 Microspheres	**Warnings**
	• HepaSphere Microspheres size must be chosen after consideration of the arteriovenous angiographic appearance. HepaSphere Microspheres size should be selected both to be appropriate for the size of the vessel feeding the target and to prevent passage from artery to vein. • Some of the HepaSphere Microspheres may be slightly outside of the range, so the physician should be sure to carefully select the size of HepaSphere Microspheres according to the size of the target vessels at the desired level of occlusion in the vasculature and after consideration of the arteriovenous angiographic appearance. • Because of the significant complications of untargeted embolization, extreme caution should be used for any procedures involving the extracranial circulation encompassing the head and neck, and the physician should carefully weigh the potential benefits of using embolization against the risks and potential complications of the procedure. These complications can include blindness, hearing loss, loss of smell, paralysis, and death.

Product Configuration	Labeling
	• Serious radiation induced skin injury may occur to the patient due to long periods of fluoroscopic exposure, large patient, angled x-ray projections and multiple image recording runs or radiographs. Refer to your facility's clinical protocol to ensure the proper radiation dose is applied for each specific type of procedure performed. • Onset of radiation injury to the patient may be delayed. Patients should be counselled on potential radiation effects, what to look for and whom to contact if symptoms occur. • HepaSphere Microspheres MUST NOT be reconstituted in sterile water for injection. Reconstitution in sterile water results in extensive swelling that renders the injection of HepaSphere Microspheres very difficult or may prevent injection. • Do not reconstitute HepaSphere Microspheres with Lipiodol / Ethiodol. • Pay careful attention for signs of untargeted embolization. During injection carefully monitor patient vital signs to include SaO2 (e.g., hypoxia, CNS changes). Consider terminating the procedure, investigating for possible shunting, or increasing Microspheres size if any signs of untargeted embolization occur or patient symptoms develop. • Consider upsizing the Microspheres if angiographic evidence of embolization does not quickly appear evident during injection of the Microspheres. ***Warnings about use of small microspheres***: • Careful consideration should be given whenever use is contemplated of embolic agents that are smaller in diameter than the resolution capability of your imaging equipment. The presence of arteriovenous anastomoses, branch vessels leading away from the target area or emergent vessels not evident prior to embolization can lead to untargeted embolization and severe complications. • Microspheres smaller than 100 microns are more likely to terminate circulation to distal tissue. Greater potential of ischemic injury results from use of smaller sized microspheres and consideration must be given to the consequence of this injury prior to embolization. The potential consequences include swelling, necrosis, paralysis, abscess and/or stronger post-embolization syndrome. • Post embolization swelling may result in ischemia to tissue adjacent to target area. Care must be given to avoid ischemia of intolerant, non-targeted tissue such as nervous tissue.
	Precautions
	• HepaSphere Microspheres must only be used by physicians trained in vascular embolization procedures. The size and quantity of microspheres must be carefully selected according to the lesion to be treated and the potential presence of shunts. Only the physician can decide the most appropriate time to stop the injection of HepaSphere Microspheres.

Product Configuration	Labeling

	• Do not use if the vial, cap, or pouch appear damaged.
	• For single patient use only - Contents supplied sterile - Never reuse, reprocess, or resterilize the contents of a vial that has been opened. Reusing, reprocessing or resterilizing may compromise the structural integrity of the device and or lead to device failure, which in turn may result in patient injury, illness or death. Reusing, reprocessing or resterilizing may also create a risk of contamination of the device and or cause patient infection or cross infection including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient. All procedures must be performed according to accepted aseptic technique.
	• HepaSphere Microspheres MUST NOT be used in their original dry state. They must be reconstituted before use.
	• HepaSphere Microspheres swell in aqueous solution. The magnitude of swelling depends on the ionic concentration of the solution. Refer to section “SWELLING BEHAVIOR” of the product’s Instructions For Use (IFU).
	• HepaSphere Microspheres are compressible and can be injected easily through microcatheters. However, injection of the HepaSphere Microspheres before they are fully expanded could result in failure to reach the intended embolization target and possible embolization of a larger tissue area.
	• Note: Maximum recommended concentration of doxorubicin HCl is 5mg/ ml. Concentrations of doxorubicin HCl above 5mg/ml substantially increase the solution viscosity and make it difficult to handle with HepaSphere Microspheres. Maximum recommended concentration of irinotecan is 20 mg/ml.
	• Patients with known allergies to non-ionic contrast media may require corticosteroids prior to embolization. Additional evaluations or precautions may be necessary in managing periprocedural care for patients with the following conditions:
	  ○ Bleeding diathesis or hypercoagulative state
	  ○ Immunocompromise
	• Note: If loading HepaSphere Microspheres with doxorubicin HCl or irinotecan, refer to the appropriate drug IFU for information concerning contraindications, warnings, precautions, potential complications, dosage, and patient management before use.

4.3 Other Relevant Safety Aspects

There have been no field corrective actions or recalls for HepaSphere Microspheres.

5.0 Summary of Clinical Evaluation and Postmarket Clinical Follow-up

5.1 Summary of Clinical Data for the Equivalent Device

Not applicable.

5.2 Summary of Clinical Investigations of the Subject Device

mCRC Registry

A post market clinical study has been implemented to provide further demonstration of the safety and effectiveness of HepaSphere Microspheres for delivery of irinotecan in clinical use for treating metastatic colorectal cancer. This registry consists in the prospective collection of clinical use data for HepaSphere Microspheres with delivery of irinotecan for the treatment of patients with metastatic colorectal cancer. A total of 105 patients have been enrolled and treated. The protocol for this study (CRC-P4-16-01 V1.0): Prospective Registry of Transarterial Chemoembolization of Metastatic Colorectal Cancer to the Liver with HepaSphere™ Microspheres loaded with irinotecan was sent to LNE-G-Med on May 10, 2016 and was approved by the Ethic Committee end of May 2016.

5.3 Summary of Clinical Data from Other Sources

A comprehensive literature review was performed to gather clinical data in support of continued CE-marking and to assist in documenting conformity with the relevant European MDR concerning device safety and performance. Literature search strategies were designed to identify articles relevant to the HepaSphere Microspheres. The results of the literature review also provide verification that all clinical hazards have been addressed in the subject device risk analysis. Both favourable and unfavourable references have been identified and summarized.

5.4 Overall Summary of Clinical Performance and Safety

The devices HepaSphere Microspheres have been used safely and effectively for:

- Embolisation of hepatocellular carcinoma
- Embolisation of metastases to the liver
- Embolisation of metastatic colorectal cancer (mCRC) to the liver

Clinical Benefits/Performance Analysis

Performance data from the HepaSphere Microspheres (HS) clinical literature data and State-Of-the-Art and Safety and Performance literature of Similar devices (SD) are summarized in Table 9 and Table 10.

Similar medical devices identified in the state-of-the-art literature used for embolotherapy, and quite like HepaSphere Microspheres are:

- DC Bead™ in EU / LC Bead™ in US (Boston Scientific)
- Lifepearl® drug elutable microspheres in EU / HydroPearl® in US (Terumo interventional systems)
- Embozene TANDEM™ Microspheres in EU / Oncozene™ Microspheres in US (Celonova/Boston scientific)

Table 9. Comparative Performance of TACE procedure in HCC and liver metastases

Device Type/Application	HepaSphere Microspheres N=1176	Similar Devices N=1387	*P*-value p1-p2 ≠ 0
Average technical success rate	98% (1152/1176)	99% (1373/1387)	$P > 0.05$
Average complete tumour response rate (at 3 months)	35% (412/1176)	30% (416/1387)	$P = 0.007$
Average objective tumor response rate (at 3months)	67% (788/1176)	64% (888/1387)	$P > 0.05$
Median progression free survival (months)	12 [Range: 8-24]	14 [Range: 2-24]	N/A
Median overall survival	27 [Range: 14-37]	25 [Range: 14-44]	N/A

Abbreviations: CI = confidence interval.
‡ Statistically significant (P<0.05)

Table 10. Comparative Performance for TACE procedure of mCRC to the Liver

Device Type/Application	HepaSphere Microspheres N=76	Similar Devices N=767	*P*-value p1-p2 ≠ 0
Average technical success rate	100% (76/76)	100% (767/767)	$P > 0.05$
Average complete tumour response rate (at 3 months)	15% (11/76)	15% (115/767)	$P = 1.0$
Average objective tumor response rate (at 3months)	55% (42/76)	56% (429/767)	$P = 0.9$
Median progression free survival (months)	5 [Range: 3-10]	8 [Range: 4-11]	N/A
Median overall survival	23 [Range: 8-38]	20 [Range: 7-25]	N/A

Abbreviations: CI = confidence interval.
‡ Statistically significant (P<0.05)

Embolization with HepaSphere Microspheres is a minimally invasive treatment that is effective for:

- Delaying disease progression and improving survival in patients with hepatocellular carcinoma and metastases to the liver
- Delaying disease progression and improving survival in patients with metastatic colorectal cancer to the liver.

The clinical benefits for the subject devices have been substantiated via objective evidence from the clinical data from literature. The ability of the subject devices to achieve the intended performances was assessed and documented. The results of the performance analysis demonstrate that the subject devices perform as intended and are State-Of-the-Art.

The published studies related to the use of HepaSphere Microspheres in HCC and liver metastases are summarized in Table 11. The published studies related to the use of HepaSphere Microspheres in mCRC to the liver are summarized in Table 12.

Table 11. HepaSphere Microspheres: Literature Summary for HCC and Liver Metastases

Author (Year) Study Design	Indication	n	Device	Drug	Follow-up (months)	Technical Success Rate	CR	ORR	DCR	PFS (months)	Median OS (months)
Gross (2008) Observational study	HCC	18	HS	Doxorubicin Epirubicin	6	100%	52%	77%	100%	ND	ND
Osuga (2008) Retrospective	HCC	59	HS	Bland	31	99%	22%	64%	96%	ND	30
Jarzabek (2011) Prospective	Liver Metastases	15	HS	Doxorubicin	2	93%	ND	27%	60%	ND	ND
Van Malenstine (2011) RCT	HCC	16	HS	Doxorubicin	2	ND	ND	ND	77%	ND	ND
Haug (2012) Case Report	HCC	1	QS†	Doxorubicin Cisplatin Mitomycin	NA	NA	NA	NA	NA	NA	NA
Idilman (2012) Retrospective	HCC	24	HS	Doxorubicin	19	100%	13%	25%	79%	ND	14
Dekervel (2013) Prospective	HCC	64	HS	Doxorubicin	14	100%	ND	45%	75%	ND	21
Dorn (2013) Retrospective	HCC	190	QS†	Doxorubicin	48	100%	43%	79%	100%	ND	22

Author (Year) Study Design	Indication	n	Device	Drug	Follow-up (months)	Technical Success Rate	CR	ORR	DCR	PFS (months)	Median OS (months)
Malagari (2013) Prospective	HCC	45	HS	Doxorubicin	16	100%	18%	69%	89%	ND	16
Moschouris (2013) Retrospective	HCC	47	HS	Doxorubicin	15	ND	11%	57%	91%	24	33
Bishay (2014) Retrospective	HCC	20	QS†	Doxorubicin	10	100%	30%	65%	95%	ND	ND
Hetta (2014) Prospective	HCC	50	HS	Doxorubicin	6	100%	42%	80%	96%	ND	ND
Klass (2014) Prospective	HCC	24	HS	Doxorubicin	1	96%	61%	65%	100%	ND	ND
Amer (2015) Prospective	HCC	52	HS	Doxorubicin	12	100%	77%	100%	100%	ND	ND
Dansey (2015) Case Report	HCC	1	QS†	Doxorubicin	NA	NA	NA	NA	NA	NA	NA
Duan (2015) Retrospective	HCC	26	QS†	Doxorubicin	3	100%	19%	54%	69%	ND	ND
Ginsburg (2015) Retrospective	HCC	89	QS†	Doxorubicin Epirubicin	56	100%	88%	94%	99%	9	39
Hiraki (2015) Prospective	HVT (various, incl. HCC)	24	HS	Bland	3	100%	ND	ND	ND	ND	ND
Kucukay (2015) Retrospective	HCC	53	HS	Doxorubicin	80	97%	ND	ND	ND	11	37
Malagari (2015) Systematic review	HCC	NA	HS	NA	NA	NA	NA	NA	NA	NA	NA
Vasnani (2016) Retrospective	HCC	42	QS†	Doxorubicin Epirubicin	ND	ND	86%	95%	95%	ND	ND
Bonne (2017) Retrospective	Liver Metastases	17	HS/QS†	Doxorubicin	3	100%	0%	82%	82%	ND	ND
Cavalcante (2017) Prospective	HCC	17	HS	Doxorubicin	2	100%	29%	65%	94%	ND	ND

Author (Year) Study Design	Indication	n	Device	Drug	Follow-up (months)	Technical Success Rate	CR	ORR	DCR	PFS (months)	Median OS (months)
Sun (2017) Prospective	HCC and liver metastases	30	HS	Doxorubicin	1	100%	7%	63%	87%	ND	ND
Zurstrassen (2017) Prospective	HCC	18	HS	Doxorubicin	6	83%	40%	53%	93%	ND	31
Malagari (2019) Prospective	HCC	142	HS	Doxorubicin	47	ND	36%	83%	96%	9	31
Chen (2020) Retrospective	HCC	51	HS	Doxorubicin	6	100%	14%	78%	94%	ND	ND
Chiu (2020) Retrospective	HCC	42	HS	Doxorubicin	12	ND	19%	60%	81%	8	24

Abbreviations: CR = complete response, DCR = disease control rate, HS = HepaSphere, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, QS = Quadrasphere
†Quadrasphere (QS) is the microsphere configuration available only in the US

Table 12. HepaSphere Microspheres Loaded with Irinotecan: Literature Summary for mCRC to the Liver

Author (Year) Study Design	Indication	n	Device	Drug	Follow-up (months)	Technical Success rate	CR	ORR	DCR	PFS (months)	Median OS (months)
Huppert (2013) Prospective	mCRC	29	HS	Irinotecan	15	100%	24%	72%	86%	5	8
Mansour (2016) Prospective	mCRC	22	HS	Irinotecan	39	100%	0%	59%	82%	ND	ND
Ranieri (2016) Prospective	mCRC	25	HS	Irinotecan	42	100%	22%	35%	87%	ND	37

Abbreviations: CR = complete response, DCR = disease control rate, ORR = objective response rate, OS = overall survival, PFS = progression-free survival

Clinical Risks/Safety Analysis

Safety data for the HepaSphere Microspheres have been analysed through a review of the peer-reviewed literature and post market data. As illustrated by the data from Table 13 and Table 14**Erreur ! Source du renvoi introuvable.**, HepaSphere Microspheres exhibit very low major and minor adverse event rates, and these rates compare favourably with those reported for other embolics in the clinical literature data and SOA literature. No new safety concerns specific to the subject device were identified in this evaluation, and the rates reported in the literature are consistent with available data for State-Of-the-Art similar devices (SD).

Table 13. Comparative Safety for HCC and liver metastases

Adverse Events in HCC From Literature search*	HS rate (N= 1176)	SD rate (N= 1387)	P -value	SOA Threshold
PES related events (Fever, Pain, Nausea, Vomiting)	38%	24%	$P < 0.001$	≤ 60%
Fatigue, loss of appetite	2%	2%	$P > 0.05$	≤ 54%
Liver enzyme abnormalities	2%	1%	$P > 0.05$	≤ 60%
Infection (including liver abscess, septicemia)	1%	1%	$P > 0.05$	≤ 3%
Acute ascites	0.6%	1%	$P > 0.05$	≤ 8%
Undesired ischemia	1%	0.1%	$P = 0.01$	≤ 5%
Acute cholecystitis, cholangitis	0.2%	1%	$P > 0.05$	≤ 13%
Acute pancreatitis	0.2%	0.2%	$P > 0.05$	-
Pulmonary embolism	0.2%	0%	$P > 0.05$	-
Pleural effusion	0.2%	0.2%	$P > 0.05$	≤ 6%
30-day mortality	0.2%	1%	$P > 0.05$	-
Allergic reaction to contrast	0.1%	1%	$P = 0.003$	-
Catheterization related complications (hematoma)	0.1%	0.1%	$P > 0.05$	≤ 6 %
Cardiac disorders	0.1%	0%	$P > 0.05$	-
Splenic infarction	0.1%	0%	$P > 0.05$	-
Hypertension	0%	2%	$P < 0.001$	-
Liver failure	0%	1%	$P = 0.02$	≤ 1.4%
Acute renal failure	0%	0%	$P > 0.05$	-

Statistically significant ($P<0.05$)
*Mean Follow-up: 16 months for HS; 16 months for SD

Table 14. Comparative Safety for mCRC to the liver

Adverse Events in mCRC From Literature search	HS rate (N= 76)	SD rate (N= 767)	P -value	SOA Threshold
PES related events	48%	35%	$P = 0.02$	≤ 60%
Fatigue, loss of appetite	20%	5%	$P < 0.001$	≤ 54%
Acute ascites	4%	0.1%	$P = 0.003$	≤ 8%
Infection (including liver abscess, septicemia)	1%	2%	$P > 0.05$	≤ 3%
Cardiac Disorder	0%	0%	$P > 0.05$	-
Splenic infarction	0%	0%	$P > 0.05$	-
Hypertension	0%	3%	$P > 0.05$	-
Catheterization related complications (hematoma)	0%	0%	$P > 0.05$	≤ 6%
Liver enzyme abnormalities	0%	13%	$P < 0.001$	≤ 60%
Liver failure	0%	1%	$P > 0.05$	≤ 1.4%
Acute renal failure	0%	0%	$P > 0.05$	-
Acute cholecystitis, cholangitis	0%	1.2%	$P > 0.05$	≤ 13%
Acute pancreatitis	0%	0.4%	$P > 0.05$	-
Allergic reaction to contrast	0%	0%	$P > 0.05$	-
pleural effusion	0%	0%	$P > 0.05$	≤ 6%
Pulmonary embolism	0%	0.1%	$P > 0.05$	-
Undesired ischemia	0%	0%	$P > 0.05$	≤ 5%
30-day mortality	0%	0.1%	$P > 0.05$	-

Statistically significant ($P<0.05$)
*Mean Follow-up: 32 months HS; 18 months SD

As illustrated by the above data, the HepaSphere Microspheres exhibit low major and minor adverse event rates, which compare favourably with those reported for comparable embolization devices and alternative therapies in the clinical literature data and SOA literature.

The HepaSphere Microspheres were deemed consistent with the benchmark devices for safety and performance in this patient population. The devices in the HepaSphere Microspheres are well established, having demonstrated acceptable safety and performance profile since first commercialization in 2006. Based on design verification/validation testing results, safety and performance outcomes in the literature, and PMS

data, there are no known uncertainties regarding safety and performance of the subject device or the intended use. The known risks are well-documented, and the risk of occurrence is low and not associated with any safety or performance signals.

When used in accordance with the IFUs, the risks associated with the use of HepaSphere Microspheres are low and outweighed by the clinical benefits associated with use. The clinical evidence demonstrate that the HepaSphere Microspheres meet the established safety and performance acceptance criteria, with a benefit-risk profile aligned with the current state-of-the-art.

5.5 Postmarket Clinical Follow-up

Clinical Evaluation Report of HepaSphere Microspheres has concluded that for the indications stated in the IFU, the evidence presented is adequate to support the long-term safety and performance of subject device.

The postmarket clinical follow-up of HepaSphere Microspheres includes the following activities:

- Screening of scientific literature
- Post Market Clinical Follow Up Study (prospective registry)

A Post Market Clinical Follow-up study is ongoing to gather more data on the safety and effectiveness of HepaSphere Microspheres for the indication transarterial chemoembolization of metastatic colorectal cancer (mCRC) to the liver, which is a more recent indication (CE-mark: 2015).

Proactive PMCF data will be collected and assessed on 105 patients among 2 sites (France and Greece). Analysis will be performed when all subjects enrolled have been followed for survival for two years, are considered lost to follow up, or have died, whichever comes first.

Effectiveness of mCRC embolization will be evaluated by the median overall survival of subjects (primary objective), objective response rate, best tumor response, median liver progression-free survival and time to progression (secondary objectives).

6.0 Therapeutic Alternatives

The therapeutic alternatives for each indication are summarized in Table 15.

Table 15. Summary of treatment options for the target population

Treatment options of HCC and metastases to the liver including mCRC		Reference
Available treatments	Treatment options and Interventions for the patients with intermediate liver tumors are the following: • Transarterial chemoembolisation (TACE) is the most widely used primary treatment for unresectable liver tumors, and it is the recommended first-line therapy for patients with intermediate-stage disease. ○ Drug eluting microspheres Transarterial chemoembolisation (DEM-TACE) ○ Conventional Transarterial chemoembolisation (cTACE) is the most widely used primary treatment for unresectable liver tumors, and it is the recommended first-line therapy for patients with intermediate-stage disease. • Selective internal radiation therapy (SIRT) also called Transarterial radioembolization (TARE)	EASL 2018
Drug eluting microspheres Transarterial chemoembolisation (DEM-TACE)		
Description	DEM TACE is a strategy allowing maximum and sustained intratumoral concentration of the chemotherapeutic agent with minimal systemic exposure, along with calibrated tumour vessel obstruction. Embolic microspheres have the ability to sequester chemotherapeutic agents and release them in a controlled mode over a one-week period.	EASL 2018
Summary of clinical benefit	Comparative data are limited to irinotecan-based drug-eluting beads in a small phase II cohort in previously treated patients showing a benefit versus systemic chemotherapy.	Van Custem 2016
Summary of clinical risk/Limits	• Refer to Figure 2.	Lencioni 2016
Transarterial radioembolization (TARE)		
Description	TARE involves the injection of implantable radioactive microspheres into tumor-feeding arteries in order to expose the tumor to highly concentrated radiation while protecting the normal parenchyma. ^{90}Y is the most commonly used radioisotope and emits high-energy and pure β-rays with a half-life of 64.2 hours. The microspheres available for 90Y infusion are 20 to 60 µm in diameter and are made of resin or glass.	KJR 2018
Summary of clinical benefit/advantages	• For patients with liver-limited metastases failing the available chemotherapeutic options, radioembolisation with yttrium-90 resin microspheres has been shown to prolong the time to tumour progression in the liver,	Hendlisz 2010
Summary of clinical risk/limits	• Specific risks related to radiation which is carcinogenic itself. (Marrero et al.2018) • Biliary stricture (4%) • Gastric Ulcer (3%) • Hypervolemia (1%) • Oesophageal varices (1%)	Marrero et al. 2018 (ASSLD guideline) Sapir 2017

AE Name	No. of Studies	Total No. of Patients	No. of Patients With AE	AE Rate Estimate	Lower 95% CI	Upper 95% CI
Fever	91	7,028	3,700	57.8	50.2	65.4
Liver enzyme abnormalities	48	9,021	3,892	52.0	43.9	60.1
PES	40	3,346	1,032	47.7	35.4	60.0
Abdominal pain	69	5,309	1,781	42.5	36.0	48.9
Fatigue/malaise	17	1,633	457	39.9	25.8	54.1
Anorexia/loss of appetite	16	1,867	691	38.0	28.5	47.6
Vomiting	49	4,754	1,297	34.2	26.9	41.4
Nausea	25	1,218	361	32.4	23.0	41.7
Hematological/bone marrow toxicity	48	11,962	2,907	28.6	25.0	32.1
Bilirubin-related abnormalities	36	5,155	985	23.5	19.7	27.3
Hepatic decompensation/deterioration of hepatic function	23	3,287	533	21.8	14.3	29.2
Elevated renal enzymes/renal dysfunction	23	2,446	434	15.1	10.4	19.9
Alopecia	11	805	113	12.9	6.8	19.1
Diarrhea	14	1,167	113	9.0	5.4	12.7
Cholecystitis	18	1,549	47	8.4	4.1	12.8
Skin ulcer/rash/erythema	12	1,390	144	8.2	5.1	11.3
Hepatic arterial complications	20	3,061	271	7.2	5.0	9.5
Ascites	22	1,805	113	6.1	4.0	8.1
Pleural effusion	12	2,056	94	4.2	2.2	6.2
Procedural complications	30	4,145	212	4.2	2.6	5.7
Hepatic encephalopathy/coma	14	1,346	44	2.0	0.9	3.2
Gastrointestinal bleeding (varices or ulcer)	44	5,721	142	1.9	1.3	2.4
Hepatic failure	31	5,837	95	1.0	0.6	1.4
Bacteremia/septicemia	17	2,301	37	1.0	0.5	1.4
Abscess	30	5,138	67	0.9	0.6	1.2
Renal failure	15	1,488	22	0.6	0.2	1.0

Figure 2. Estimated Rate of Individual AEs as Assessed in the Safety Analysis (Source: Lencioni 2016)

Table 16. Summary of other treatment options

Intervention	Specification	Reference
Surgical resection		
Description	Surgical resection of the tumours by laparoscopy or open surgery	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical benefit	• For patients with single tumours, well-preserved organ function, and no evidence of portal hypertension. Surgical resection offers a low perioperative mortality and is associated with survival rates of nearly 70% at 5 years. • There is technically no size cut-off for tumour diameter, and large tumours can be safely resected if there is sufficient functional remnant tissue.	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical risk	• The risk of recurrence following resection is up to 70% at 5 years, with the most important predictors being tumour differentiation, micro- and macrovascular invasion, and the presence of satellite nodules.	Marrero et al. 2018 (ASSLD guideline)
Target population	Surgical resection is the treatment of choice for resectable HVT and HCC occurring in patients without cirrhosis, which accounts for 5%-10% of HCC in Western countries.	Marrero et al. 2018 (ASSLD guideline)
Transplantation		
Description	Transplantation of the target organ (e.g., liver) to the patient.	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical benefit	• Transplantation is a highly effective, efficient therapy for early-stage HCC because it offers optimal treatment of both the underlying liver disease and the tumour, and is associated with excellent long-term survival rates for HCC within Milan criteria occurring in the setting of decompensated liver disease.	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical risk	• Transplantation is limited by the extreme shortage of available organ allografts and the need for lifelong immunosuppression.	Marrero et al. 2018 (ASSLD guideline)
Target population	Patients with early-stage liver tumours.	Marrero et al. 2018 (ASSLD guideline)
Thermal ablation		
Description	Destruction or ablation of tumour cells can be achieved by the injection of chemical substances (ethanol, acetic acid, and boiling saline) or by modifying local tumour temperature (radiofrequency [RFA], microwave, laser, cryotherapy). The procedure can be done percutaneously with minimal invasiveness or during laparoscopy and is currently considered the best option for patients with BCLC stage A who are not candidates for surgical intervention.	Marrero et al. 2018 (ASSLD guideline)
Summary of clinical benefit	Several randomized controlled trials (RCTs) have confirmed the superiority of RFA over ethanol injection in terms of survival, particularly in BCLC stage A with nodules between 2 and 4 cm. Thermal ablative techniques have the best efficacy in tumours with maximum diameter less than	Marrero et al. 2018 (ASSLD guideline)

Intervention	Specification	Reference
	3 cm, although microwave ablation potentially provides better tumoral response than RFA.	
Summary of clinical risk/Limits	• The recurrence rate after thermal ablation is similar to that observed after surgical resection, • It has been shown that local recurrence is related to size and higher with tumours that are >3 cm • HCC recurrence can occur at new sites in the liver in around 40% of individuals.	Marrero et al. 2018 (ASSLD guideline)
Target population	Patients with BCLC stage A who are not candidates for surgical intervention.	Marrero et al. 2018 (ASSLD guideline)

7.0 Suggested profile and training for users

HepaSphere Microspheres must only be used by specialist physicians trained in vascular embolisation procedures.

8.0 Applicable Standards and Common Specifications

The list of all applied common specifications (CS), international standards harmonized under the medical device directives and/or the MDR, and relevant adopted monographs of the European pharmacopoeia is provided in Table 17.

Table 17. Applicable Standards and Common Specifications

Standard Title	State of the Art Date/Version
Medical devices – Information to be supplied by the manufacturer	NF EN 1041:2008+A1:2013
Information Supplied by the Manufacturer with Medical Devices	ISO 20417:2021
Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	NF EN ISO 15223-1:2017
Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements	ISO 15223-1:2021
Medical devices — Symbols to be used with medical device labels, labelling, and information to be supplied — Part 2: Symbol development, selection and validation	NF EN ISO 15223-2:2010
Guidance document Implant Card relating to the application of Article 18 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices	MDCG 2019-8 v2 (2020)
Classification of Air Cleanliness, Clean rooms & Associated Controlled Environments. Part 1: Classification of air cleanliness	NF EN ISO 14644-1:2016

Standard Title	State of the Art Date/Version
Sterilization of health care products -- Microbiological methods -- Part 1: Determination of a population of microorganisms on products	NF EN ISO 11737-1:2018
Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process	NF EN ISO 11737-2:2010
Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process	NF EN ISO 11737-2:2020
Bacterial Endotoxins Assay	EP 2.6.14 and USP <85>
Transfusion and Infusion Assemblies and Similar Medical Devices	USP <161>
Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" – Part 1: Requirements for terminally sterilized medical devices	NF EN 556-1:2002
Sterilization of health care products -- Radiation -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	NF EN ISO 11137-1:2016/A2:2019
Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose	NF EN ISO 11137-2:2015
Quality Systems – Medical Devices – Quality Management Systems. Requirements for Regulatory Purposes	ISO 13485:2016 EN ISO 13485:2016
Medical Devices - Application of Risk Management to Medical Devices	NF EN ISO 14971:2019
Biological Evaluation of Medical Devices – Part 1: Evaluation and testing	NF EN ISO 10993-1:2020
Biological evaluation of medical devices -- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity	NF EN ISO 10993-3:2014
Biological evaluation of medical devices -- Part 4: Selection of tests for interactions with blood	NF EN ISO 10993-4:2018
Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity	NF EN ISO 10993-5:2010
Biological Evaluation of Medical Devices – Part 6: Tests for local effects after implantation	NF EN ISO 10993-6:2017
Biological evaluation of medical devices -- Part 10: Tests for irritation and skin sensitization	NF EN ISO 10993-10:2013
Biological evaluation of medical devices -- Part 11: Tests for systemic toxicity	NF EN ISO 10993-11:2018
Biological Evaluation of Medical Devices – Part 12: Sample preparation and reference materials	ISO 10993-12:2021
Biological Evaluation of Medical Devices – Part 17: Methods for the Establishment of Allowable Limits for Leachable Substances	NF EN ISO 10993-17:2009
Biological Evaluation of Medical Devices – Part 18: Chemical Characterization of Medical Device Materials within a Risk Management Process	NF EN ISO 10993-18: 2020
Biological Evaluation of Medical Devices – Part 19: Physico-chemical, morphological and topographical characterization of materials	ISO/TS 10993-19:2020

Standard Title	State of the Art Date/Version
Biological evaluation of medical devices — Part 23: Tests for irritation	ISO 10993-23:2021
Clinical investigation of medical devices for human subjects -- Good clinical practice	NF EN ISO 14155:2020
Guidelines on Medical Devices – Clinical Evaluation – A Guide for Manufacturers and Notified Bodies under Directives 93/42/EEC	MEDDEV2.7.1 Rev. 4 (Jun 2016)
Guidance on Summary of safety and clinical performance	MDCG 2019-9 (August 2019)
Guidance on sufficient clinical evidence for legacy devices	MDCG 2020-6 (April 2020)
Guidance on PMCF plan template	MDCG 2020-7 (April 2020)
Guidance on Clinical evaluation assessment report template	MDCG 2020-13 (July 2020)
Post Market Clinical Follow-up studies	MEDDEV 2.12/2 Rev. 2 (Jan 2012)
Non-active surgical implants -- General requirements	NF EN ISO 14630:2013
Injection containers and accessories — Part 6: Caps made of aluminum-plastics combinations for injection vials	NF EN ISO 8362-6:2011
Containers – Plastic (vial)	USP <661>
Polyolefins (vial)	EP 3.1.3
Elastomeric closures for injections (grey rubber stopper)	USP <381>
Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders (grey rubber stopper)	EP 3.2.9
Medical Devices – Application of usability engineering to medical devices	IEC 62366-1:2015/Amd 1:2020
Packaging for Terminally Sterilized Medical Devices. Part 1: Requirements for materials, sterile barrier systems, and packaging systems.	NF EN ISO 11607-1:2020
Packaging for Terminally Sterilized Medical Devices. Part 2: Validation requirements for forming, sealing and assembly processes	NF EN ISO 11607-2:2020
Standard Practice for Performance Testing of Shipping Containers and Systems	ASTM D4169 - 16
Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test)	ASTM F2096 - 11 (2019)
Standard Test Method for Seal Strength of Flexible Barrier Materials	ASTM F88/F88M - 15
Standard Test Methods for Internal Pressurization Failure Resistance of Unrestrained Packages for Medical Applications	ASTM F1140/F1140M-13 (2020)
Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices	ASTM F1980 - 16
Guidelines on a Medical Devices Vigilance System	MEDDEV 2.12/1 Rev. 8 (Jan 2013)

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10.0 List of abbreviations

Abbreviation/Acronym	Definition
BCLC	Barcelona Clinic Liver Cancer
CR	Complete tumor Response
DCR	Disease Control Rate
DEM	Drug Eluting Microspheres
EEC	European Economic Community
ER	Essential Requirements
EU	European Union
HCC	Hepatocellular Carcinoma
HS	HepaSphere Microspheres
IFU	Instruction For Use
Lm	Liver metastases
LT	Liver Transplantation
mCRC	Metastatic Colorectal Cancers
MDR	Medical Device Regulation
MR	Magnetic Resonance
ORR	Objective tumor Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PMCF	Post Market Clinical Follow-up
PMS	Post Market Surveillance
QS	QuadraSphere Microspheres
SD	Similar Device
SOA	State-of-the-art
TACE	Transarterial ChemoEmbolization

11.0 Revision History

SSCP Revision	ECN Number	Date Issued	Change description	SSCP Author/PRRC	Revision Validated by the Notified Body
001	PAR4219	21-Feb-2023	Initial release of the Summary of Safety and Clinical Performance (SSCP) for the HepaSphere Microspheres	Author: **Lionel Ekedi Ngando** Person Responsible for Regulatory Compliance: **Rosène Amossé**	☒ Yes Validation language: English ☐ No

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Summary of Safety and Clinical Performance (SSCP)

Language: English

This document is a summary of safety and clinical performance (SSCP) for the HepaSphere Microspheres intended for public access to the main aspects related to device safety and performance. The information presented in this SSCP is intended for patients or lay persons. A more extensive summary of device safety and clinical performance is provided for healthcare professionals.

The SSCP is not intended to give general advice on the treatment of a medical condition. Please contact your doctor or healthcare professional if you have questions about your medical condition or about the use of the HepaSphere Microspheres in your situation. This SSCP is not intended to replace an Implant Card or the Instructions for Use (IFU) to provide information on the safe use of the HepaSphere Microspheres.

1.0 Device Identification and General Information

HepaSphere Microspheres were first CE-marked by Biosphere Medical in 2004 for the embolization of liver cancer and metastases to the liver. Chemoembolization with HepaSphere Microspheres loaded with doxorubicin for liver cancer and liver metastases received CE-mark in 2007. More recently, HepaSphere Microspheres loaded with irinotecan has been approved for embolization of metastatic colorectal cancer (mCRC) to the liver (CE-mark in 2015).

1.1 Device trade name(s):

HepaSphere® Microspheres is the device trade name covered by this SSCP. The device model numbers are listed in Table 1.

Table 1 Devices Included in this SSCP

Nominal dry size (µm)	Size after Reconstitution (µm)	Colour code	Reference code by weight	
			25 mg vial	50 mg vial
20-40*	80-160	Grey*	V125HS*	V150HS*
30-60	120-240	Orange	V225HS	V250HS
50-100	200-400	Yellow	V325HS	V350HS
100-150	400-600	Blue	V525HS	V550HS
150-200	600-800	Red	V725HS	V750HS

*HepaSphere Q2 Microspheres is also a brand name of the 20-40µm size range

1.2 Manufacturer Information

The name and address of the manufacturer of the HepaSphere Microspheres are provided in Table 2.

Table 2 Manufacturer Information

Manufacturer Name	Address of Manufacturer
Biosphere Medical S.A.	Parc des Nations – Paris Nord II, 383, Rue de la Belle Etoile, 95700 Roissy en France, France

1.3 Basic UDI-DI

The basic Unique Device Identifier (UDI) with Device Identification (DI) key is 088445048755E9.

1.4 Year of EU Market Introduction

The HepaSphere Microspheres were first placed on the EU market in 2004.

2.0 Intended Use of the Device

2.1 Intended Purpose

HepaSphere Microspheres are designed for controlled, targeted embolization. In other words, the spheres are implants. They are used to block blood flow in aimed vessels. They are used by doctor to treat liver cancers.

2.2 Indication(s) and Intended Patient Groups

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

2.3 Contraindications:

HepaSphere Microspheres have the contraindications listed below. In summary, the device is contraindicated if the treatment cannot be supported by the patient, treatment is unsafe due to other patient conditions, cancer is in the lungs, heart, or central nervous system, or if the patient has a known allergy to the device materials.

- Patients intolerant to vascular occlusion procedures
- Vascular anatomy or blood flow precluding correct catheter placement or embolic injection
- Presence or suspicion of vasospasm
- Presence or likely onset of haemorrhage

- Presence of severe atheromatous disease
- Presence of collateral vessel pathways potentially endangering normal territories during embolization
- High flow arteriovenous shunts or fistulae with luminal diameter greater than the selected size of HepaSphere Microspheres
- Vascular resistance peripheral to the feeding arteries precluding passage of HepaSphere Microspheres into the lesion
- Do not use in pulmonary vasculature, coronary and central nervous system vasculature
- Known sensitivity to poly vinyl alcohol-co-sodium acrylate

3.0 Device Description

HepaSphere Microspheres are an implant. Each microsphere is a small sphere. It is about the size of a grain of sand. It is made of acrylic copolymer. This material is safe for use in the human body. The spheres can absorb and release anticancer drugs.

3.1 Materials/Substances in Contact with Patient Tissues

Only the spheres composed of acrylic copolymer will be in contact with your blood vessels. The spheres are a life-long permanent implant.

Table 3. Contact with Materials/Substances

Material	Duration of exposure	Level of patient exposure
Poly vinyl alcohol-co-sodium acrylate	Permanent	≤ 50 mg

3.2 Operating Principals/Mode of Action

The general procedure steps and operating principle in an embolization procedure are listed in Table 4.

Table 4. Procedure and Operating Principle

Embolization Procedure	Description
Step 1	The treatment consists in blocking the target vessels with spheres mixed with anti-cancer drugs. It starts with a small cut in your thigh or your forearm.
Step 2	Using special equipment, the doctor passes a thin tube into a vessel in your thigh or your forearm.
Step 3	Then the doctor guides the tube near the location of the target vessels.

Embolization Procedure	Description
Step 4	At this location, the injection of the drug-loaded spheres begins.
Step 5	The small spheres will block the blood flow around the targeted cancer and release the anti-cancer drug.
Operating Principle	The small spheres block the vessels around the targeted cancer. Then, the blood flow cannot feed the cancer anymore. In addition, the spheres release the anti-cancer drugs. The lack of blood and the anti-cancer drugs result in the cancer decrease. In all cases, the spheres remain in the body for the lifetime of the patient. The doctor removes the tube after treatment. The doctor will apply a pressure point to stop any bleeding. The treatment is usually an outpatient procedure. The patient may be back at home within 4 to 23 hours after treatment.

3.3 Accessories

Other accessories used with the HepaSphere Microspheres during the procedure include sterile microcatheters and syringes. These accessories allow your doctor to reach the target vessel in your body and deliver the spheres to the treatment area.

3.4 Devices/Materials Used in Combination

Chemotherapy agents may be used in combination with the HepaSphere Microspheres during the procedure. These may include agents such as doxorubicin or irinotecan. Contact your doctor for more information on these agents.

4.0 Risks and Warnings

Contact your doctor if you believe that you are experiencing side effects related to the device or its use, or if you are concerned about risks. This document is not intended to replace a meeting with your doctor.

4.1 Residual Risks and Undesirable Effects

Potential complications and side effects may be associated with the HepaSphere Microspheres. These are listed in Table 5 and Table 6.

Table 5. Listing of Potential Complications

Product Configuration	Potential Complications
HepaSphere Microspheres HepaSphere Q2 Microspheres	Vascular embolization is a high-risk procedure. Complications may occur at any time during or after the procedure, and may include, but are not limited to, the following: • Post-embolization syndrome (such as nausea, vomiting, pain, fever) • Fatigue and loss of appetite • Hypertension (high blood pressure) • Liver disorders or failure (including liver enzyme anomalies and ascites) • Complications related to catheterization (e.g., haematoma at the site of entry, clot formation at the tip of the catheter and subsequent dislodgement, and nerve and/or circulatory injuries which may result in leg injury) • Vessel or lesion rupture and hemorrhage (bleeding) • Vasospasm (constriction of vessels) • Recanalisation (blood flow through treated region) • Allergic reaction to medications (e.g., analgesics) • Allergic reaction to non-ionic contrast media or embolic material • Undesirable reflux or passage of HepaSphere Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds, such as the internal carotid artery, pulmonary, or coronary circulation • Pulmonary embolism due to arteriovenous shunting • Pleural effusion • Ischemia at an undesired location, including ischemic stroke, ischemic infarction (including myocardial infarction), and tissue necrosis • Capillary bed occlusion and tissue damage (cholecystitis, cholangitis, pancreatitis) • Paralysis resulting from untargeted embolization or ischemic injury from adjacent tissue oedema • Blindness, hearing loss, and loss of smell • Foreign body reactions necessitating medical intervention • Infection necessitating medical intervention (including liver abscess) • Death

Table 6. Summary of Side Effects

Side effect	Description	Reported Frequency
Post-embolisation syndrome	Pain, fever, nausea, and tiredness.	Four out of 10 cases
Allergic reactions	Allergic reaction to gelatin, or to other products and drugs used during the treatment.	Less than one in 100 cases
Risks related to catheter placing	Damage to the blood vessel, bleeding at the cutting site or infection.	Less than one in 100 cases
Non-targeted embolisation	The small spheres may unwillingly block the blood flow of other vessels.	One in 100 cases

4.2 Warnings and Precautions

Table 7 lists the warning and precautions for the HepaSphere Microspheres.

Table 7. Listing of Warnings and Precautions

Product Configuration	Labeling
HepaSphere Microspheres HepaSphere Q2 Microspheres	**Warnings** • HepaSphere Microspheres size must be chosen after consideration of the arteriovenous angiographic appearance. HepaSphere Microspheres size should be selected both to be appropriate for the size of the vessel feeding the target and to prevent passage from artery to vein. • Some of the HepaSphere Microspheres may be slightly outside of the range, so the physician should be sure to carefully select the size of HepaSphere Microspheres according to the size of the target vessels at the desired level of occlusion in the vasculature and after consideration of the arteriovenous angiographic appearance. • Because of the significant complications of untargeted embolization, extreme caution should be used for any procedures involving the extracranial circulation encompassing the head and neck, and the physician should carefully weigh the potential benefits of using embolization against the risks and potential complications of the procedure. These complications can include blindness, hearing loss, loss of smell, paralysis, and death. • Serious radiation induced skin injury may occur to the patient due to long periods of fluoroscopic exposure, large patient, angled x-ray projections and multiple image recording runs or radiographs. Refer to your facility's clinical protocol to ensure the proper radiation

Product Configuration	Labeling
	dose is applied for each specific type of procedure performed. • Onset of radiation injury to the patient may be delayed. Patients should be counselled on potential radiation effects, what to look for and whom to contact if symptoms occur. • HepaSphere Microspheres MUST NOT be reconstituted in sterile water for injection. Reconstitution in sterile water results in extensive swelling that renders the injection of HepaSphere Microspheres very difficult or may prevent injection. • Do not reconstitute HepaSphere Microspheres with Lipiodol / Ethiodol. • Pay careful attention for signs of untargeted embolization. During injection carefully monitor patient vital signs to include SaO_2 (e.g., hypoxia, CNS changes). Consider terminating the procedure, investigating for possible shunting, or increasing Microspheres size if any signs of untargeted embolization occur or patient symptoms develop. • Consider upsizing the Microspheres if angiographic evidence of embolization does not quickly appear evident during injection of the Microspheres. ***Warnings about use of small microspheres***: • Careful consideration should be given whenever use is contemplated of embolic agents that are smaller in diameter than the resolution capability of your imaging equipment. The presence of arteriovenous anastomoses, branch vessels leading away from the target area or emergent vessels not evident prior to embolization can lead to untargeted embolization and severe complications. • Microspheres smaller than 100 microns are more likely to terminate circulation to distal tissue. Greater potential of ischemic injury results from use of smaller sized microspheres and consideration must be given to the consequence of this injury prior to embolization. The potential consequences include swelling, necrosis, paralysis, abscess and/or stronger post-embolization syndrome. • Post embolization swelling may result in ischemia to tissue adjacent to target area. Care must be given to avoid ischemia of intolerant, non-targeted tissue such as nervous tissue.
	Precautions
	• HepaSphere Microspheres must only be used by physicians trained in vascular embolization procedures. The size and quantity of microspheres must be carefully selected according to the lesion to be treated and the potential presence of shunts. Only the physician can decide the most appropriate time to stop the injection of HepaSphere

Product Configuration	Labeling
	Microspheres. • Do not use if the vial, cap, or pouch appear damaged. • For single patient use only - Contents supplied sterile - Never reuse, reprocess, or resterilize the contents of a vial that has been opened. Reusing, reprocessing or resterilizing may compromise the structural integrity of the device and or lead to device failure, which in turn may result in patient injury, illness or death. Reusing, reprocessing or resterilizing may also create a risk of contamination of the device and or cause patient infection or cross infection including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient. All procedures must be performed according to accepted aseptic technique. • HepaSphere Microspheres MUST NOT be used in their original dry state. They must be reconstituted before use. • HepaSphere Microspheres swell in aqueous solution. The magnitude of swelling depends on the ionic concentration of the solution. Refer to section “SWELLING BEHAVIOR” of the product’s Instructions For Use (IFU). • HepaSphere Microspheres are compressible and can be injected easily through microcatheters. However, injection of the HepaSphere Microspheres before they are fully expanded could result in failure to reach the intended embolization target and possible embolization of a larger tissue area. • Note: Maximum recommended concentration of doxorubicin HCl is 5mg/ ml. Concentrations of doxorubicin HCl above 5mg/ml substantially increase the solution viscosity and make it difficult to handle with HepaSphere Microspheres. Maximum recommended concentration of irinotecan is 20 mg/ml. • Patients with known allergies to non-ionic contrast media may require corticosteroids prior to embolization. Additional evaluations or precautions may be necessary in managing periprocedural care for patients with the following conditions: o Bleeding diathesis or hypercoagulative state o Immunocompromise • Note: If loading HepaSphere Microspheres with doxorubicin HCl or irinotecan, refer to the appropriate drug IFU for information concerning contraindications, warnings, precautions, potential complications, dosage, and patient management before use.

4.3 Magnetic Resonance Imaging

There is no risk with magnetic resonance imaging (MRI). The spheres are considered MRI safe.

4.4 Other Relevant Safety Aspects

There have been no product recalls or field actions related to the spheres.

4.5 Patient Implant Card

An implant card has been provided to you by the hospital after your treatment. You must keep it forever.

5.0 Summary of Clinical Evaluation and Postmarket Clinical Follow-up (PMCF)

Doctors in Europe and worldwide have used HepaSphere Microspheres for more than 15 years. Table 8 summarizes the clinical safety and performance information. These results are based on 30 clinical papers reporting use in patients to treat liver cancer.

Table 8. Safety and Performance Summary

Treatment	Analysis	Most common side effect	Serious side effect
Liver cancer	• 50% to 60% of patients show an improvement with respect to liver cancer progression. • Overall improvement in the post-treatment survival period	Pain, fever, nausea, and tiredness.	Unintended vessel blockage or infection. Less than one out of hundred cases.

When used as instructed, the risks from the use of HepaSphere Microspheres to treat liver cancers are low and outweighed by the clinical benefits. The benefit-risk ratio is favourable in all indications for use.

Each year, Biosphere Medical collects additional information from the scientific literature to confirm the continued safety and performance of the spheres. Biosphere Medical is also conducting a clinical study of 105 patients among 2 sites (France and Greece), to gather more data on the safety and effectiveness metastatic colorectal cancer to the liver.

6.0 Diagnostic or Therapeutic Alternatives

Surgical tumor resection or liver transplantation are other treatments options. Contact your doctor to discuss treatment options.

7.0 Suggested profile and training for users

The HepaSphere Microspheres should only be used by doctors trained in embolic procedures.

8.0 Readability Score

The readability of the patient-directed SSCP was assessed using the validated readability statistics reported by Microsoft Word for Office 365 MSO (Version 2022 Build 16.0.14931.20648) 32-bit. The statistics are summarized in Table 9. When combined with appropriate consultation with their doctor, these readability scores are considered acceptable for conveying necessary information to the patient.

Table 9. Readability Score Summary

Statistic	Readability Score
Flesch Reading Ease	50.7
Flesch-Kincaid Grade Level	8.9
Passive sentence percentage	27.2%