English

HepaSphere™

Microspheres

INSTRUCTIONS FOR USE

Note: *This IFU is for bland embolization only (without drug loading), such as in China.*

INTENDED USE

HepaSphere™ Microspheres are intended for use in embolization of blood vessels.

INDICATIONS FOR USE

HepaSphere™ Microspheres are indicated for use for therapeutic or preoperative purposes in the following procedures:

- Embolization of hepatocellular carcinoma
- Embolization of metastases to the liver.

DESCRIPTION

HepaSphere Microspheres are part of a family of embolic agents based on proprietary technologies. HepaSphere Microspheres are biocompatible, hydrophilic, non-resorbable, expandable, and conformable microspheres.
HepaSphere Microspheres swell upon exposure to aqueous solutions. They are available in a range of sizes.

Dry(µm)	20-40	30-60	50-100	100-150	150-200

HepaSphere Microspheres are made of 100% of poly (vinyl alcohol-co-sodium acrylate).

IMPLANTABLE DEVICE MATERIALS TABLE

Material	**Duration of exposure**	**Level of patient exposure** (for one vial)
Poly vinyl alcohol-co-sodium acrylate	Long-Term (> 30days)	15 mg, 25 mg or 50 mg

DEVICE PACKAGING

HepaSphere Microspheres are contained in a sterile, 10 ml vial, with a crimped cap, packaged in a sealed pouch.
Contents: 15 mg, 25 mg or 50 mg of dry HepaSphere Microspheres per vial to be reconstituted before use.

CLINICAL PERFORMANCE

HepaSphere Microspheres are designed for controlled, targeted embolization.
HepaSphere Microspheres are non-resorbable, long-term implant which provide permanent embolization.
HepaSphere Microspheres are conformable and expandable microspheres which adapt their morphology to the target vessel, allowing a complete occlusion of blood flow. Deprivation of blood supply to the tumor results in tumor necrosis.

CLINICAL BENEFITS

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

For a copy of this device's current European Summary of Safety and Clinical Performance (SSCP), please go to the European database on medical devices (Eudamed), where it is linked to the basic UDI-DI. https://ec.europa.eu/tools/eudamed. Basic UDI-DI: 088445048755E9. Alternatively, download a copy of the SSCP from: https://www.merit.com/sscp/

MAGNETIC RESONANCE IMAGING

HepaSphere Microspheres are made of an acrylic copolymer and are magnetic resonance imaging (MRI) compatible.

CONTRAINDICATIONS

- 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

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 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 specialist 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.

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".
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.

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

POTENTIAL COMPLICATIONS

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
- 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
- Additional information is found in the Warnings section

SWELLING BEHAVIOR

HepaSphere Microspheres swell during reconstitution with NaCl 0.9% aqueous solution and non-ionic contrast media. When hydrated in 100% NaCl 0.9% aqueous solution, or 50% non-ionic contrast and 50% NaCl 0.9% aqueous solution, HepaSphere Microspheres swell approximately 4 times their original dry diameter in approximately 10 minutes. For example, HepaSphere Microspheres with a diameter of approximately 50-100 microns in their dry state will expand to approximately 200-400 microns during reconstitution as recommended below. Because of the inherent variability of the swelling process, some of the HepaSphere Microspheres will be slightly outside of this range after reconstitution, 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 the nature of the aqueous solution.

CATHETER COMPATIBILITY

HepaSphere Microspheres can be injected with microcatheters with the following specifications:

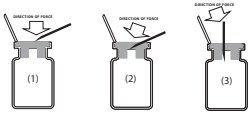
Dry (µm)	Approximate Reconstituted Size range (µm)	Catheter Size ID(in.)
20-40	80-160	≥0.020
30-60	120-240	≥0.021
50-100	200-400	≥0.021
100-150	400-600	≥0.024
150-200	600-800	≥0.027

INSTRUCTIONS FOR USE

HepaSphere Microspheres must be reconstituted following the below descriptions of OPTION 1, OPTION 2 or OPTION 3 before positioning the catheter.

- 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 the nature of the aqueous solution. See the description of "SWELLING BEHAVIOR".
- Ensure the compatibility of the HepaSphere Microspheres with the intended size of catheter to be used. See the table above.
- Inspect the packaging to confirm that it is intact. The external surface of the vial is sterile.
- According to aseptic technique, open the peel-away film beginning at the tip, and peel back the film completely to the base. Gently tip the sterile vial on the sterile field, avoiding contact with any parts previously sealed.
- HepaSphere Microspheres may be present outside the vial. Therefore, the vial must be aseptically handled away from the main sterile field.
- To prevent coring the rubber stopper, insert the injection needle as follows

1. Hold the needle so that the bevel faces upwards and position the tip diagonally to the insertion site. Press the tip against the centre of the insertion site.
2. Apply a gentle force to the needle in the opposite direction to the bevel to ease the needle into the insertion site until the heel section of the needle is no longer visible. Be careful not to scrape off the upper-facing surface of the rubber cap with the heel of the needle tip.
3. Continuing to apply a gentle force to the needle in the opposite direction to the bevel, slowly insert the needle vertically through the rubber cap.



4. After preparation, carefully examine the solution to determine if there are any rubber impurities present. If the solution appears contaminated, do not use it.

Note: The use of vented spike / blunt needles is recommended.

PREPARATION FOR EMBOLIZATION

The approximate reconstitution time is 10 min.

- Fill a syringe with 10ml of NaCl 0.9% aqueous solution. Connect the syringe to a needle of 20 gauge diameter or larger.
- To ensure proper reconstitution of the HepaSphere Microspheres, grasp the vial horizontally in your fingertips and roll the vial several times. This will transfer the dry contents of the vial to the sidewall.

Note: Pull back only the flip-top cap; do not remove the crimp ring or the stopper from the vial.

- Carefully insert the needle from the syringe through the stopper of the vial. Continue rolling the vial in your fingertips and inject the full amount (10ml) of reconstitution medium into the vial, then place the vial vertically and carefully remove the syringe with the needle attached.

Note: The vial is hermetically closed. If aspiration from the syringe into the vial does not automatically occur, then, using caution, manually aspirate air from the vial into the syringe prior to injecting the reconstitution fluid. Proper aspiration and/ or venting techniques, as approved by the healthcare facility, may be used for easier injection of reconstitution medium into vial. If aspiration of air from the vial is performed prior to reconstitution, exercise caution not to remove the spheres from the vial.

- To ensure a homogeneous reconstitution of the HepaSphere

Microspheres, shake the vial back and forth so that the liquid contacts the stopper 5-10 times.
- Wait a minimum of 10 minutes to allow the HepaSphere Microspheres to reconstitute and expand fully.
- Use a 30ml syringe and 20 gauge or larger needle to aspirate the contents of the vial. Rotate the vial to a vertical position with the bottom of the vial facing upward. Pull the needle back so that it is submerged in the liquid but not occluded by the stopper. Aspirate the entire contents of the vial into the syringe.
- 10ml of non-ionic contrast medium must be added to the syringe containing the HepaSphere Microspheres for visualization under fluoroscopy and microspheres suspension.

Note: If the air was previously aspirated from the vial, gentle injection of air using the syringe prior to aspirating the contents of the vial will ensure an easier aspiration of vial contents into the syringe. If all contents are not withdrawn, introduce an additional volume of air and repeat the aspiration process. It is possible to add an additional amount of non-ionic contrast or NaCl 0.9% aqueous solution into the syringe in order to get a higher dispersion of microspheres.

DELIVERY INSTRUCTIONS
- Carefully evaluate the vascular network associated with the target lesion utilizing high resolution imaging.

Note: It is important to determine if any arteriovenous shunts are present before beginning embolization.
- Using standard techniques, position the delivery catheter within the target vessel and the catheter tip as close as possible to the embolization target.
- Use an injection syringe no larger than 3ml for the delivery of HepaSphere Microspheres. Use of a 1ml injection syringe is recommended.
- Aspirate the HepaSphere Microspheres mixture into the injection syringe.
- Two methods for embolic aliquot sequestering for injection may be used:
- **Option 1:** Connect a 3way-stopcock to the syringe containing HepaSphere Microspheres and to the infusion micro catheter, and use a 1ml syringe for injection through the open port of the 3 way-stopcock.
  Option 2: Serial aliquots of HepaSphere Microspheres can be drawn from the syringe into a 1ml injection syringe through a 3 way-stop cock that is not attached to the infusion catheter. The 1ml syringe containing each aliquot can be attached independently to the infusion microcatheter and injected.
- Shake the syringe back and forth to maintain the homogenous suspension of the HepaSphere Microspheres mixture.
- Under continuous fluoroscopic guidance, inject the aliquot of HepaSphere Microspheres in a slow, non forceful, pulsatile manner over a time period of approximately 1 minute per ml of microspheres solution. Always inject under free-flow conditions and monitor for reflux.

Note: Reflux of embolic spheres can induce immediate ischemia of untargeted tissues and vessels.
- When stasis in the feeding pedicle occurs while delivering the HepaSphere Microspheres, wait a minimum of 5 minutes then perform a selective angiogram after the full 5 minutes wait to verify the cessation of antegrade flow.
- If cessation of antegrade flow has not occurred, continue infusion under fluoroscopic guidance until the desired devascularization is obtained.
- After the HepaSphere Microsphere infusion is completed, remove the catheter while maintaining gentle aspiration to avoid dislodging any residual HepaSphere Microspheres that may still be in the catheter lumen. Discard the catheter after removal and do not reuse.
- Discard any open vial or unused HepaSphere Microspheres.

CAUTION
In the event that the catheter becomes obstructed or significant infusion resistance is encountered during injection, do not attempt to flush the catheter with excessive pressure because reflux of embolic material may occur resulting in untargeted embolization. Remove the catheter while applying gentle aspiration and discard.

CONSERVATION / STORAGE / DISPOSAL
- HepaSphere Microspheres must be stored at room temperature in a dry, dark place in their original vials and packaging.
- Use by the date indicated on the labeling.

- Do not resterilize
- When the procedure of reconstitution is completed, store the solution of HepaSphere Microspheres in 2 to 8°C conditions and use within 24 hours, if not used immediately. Do not store HepaSphere Microspheres after contrast medium has been added.
- After use, HepaSphere Microspheres must be disposed as per hospitals contaminated waste circuit.

PATIENT COUNSELING INFORMATION

- Patients should have a clear understanding prior to embolization of who will provide their post procedure care and whom to contact in case of an emergency after embolization.
- Embolization patients should have an understanding of the potential benefits, risks, and adverse events associated with embolization. In particular, patients should understand that there is a chance their symptoms will not improve following embolization.

Size of dry products (µm)	Colour code (label borders)	Quantity of microspheres (mg)	Reference
20-40	Gray	15 25 50	V 115 HS V 125 HS V 150 HS
30-60	Orange	15 25 50	V 215 HS V 225 HS V 250 HS
50-100	Yellow	15 25 50	V 315 HS V 325 HS V 350 HS
100-150	Blue	25 50	V 525 HS V 550 HS
150-200	Red	25 50	V 725 HS V 750 HS

Note: HepaSphere Microspheres 20-40µm (size of dry product) is marketed under two names: HepaSphere Microspheres and HepaSphere Q2 Microspheres.

INFORMATION ON PACKAGING

	Manufacturer
	Date of manufacture: YYYY-MM-DD
	Use by date: YYYY-MM-DD
	Lot number
	Catalog number
	Do not resterilize
	Do not use if package is damaged and consult instruction for use
	Keep away from sunlight
	Keep dry
	Single use
	Caution
	Non-pyrogenic
	Sterilized using irradiation
	Medical Device
	Unique Device Identifier
	Single sterile barrier system with protective packaging inside
	Consult Instructions for Use
	Patient identification
	Healthcare centre or doctor
	Date
	Patient information website
CE	EC mark logo - Notified body identification: 0459
	Size of dry microspheres / Size of hydrated microspheres

In the European Union, any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the applicable Member State.

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