INSTRUCTIONS FOR USE

BioPearl™ Microspheres

STERILE • SINGLE USE ONLY • NON-PYROGENIC

Carefully read all instructions prior to use.

DESCRIPTION:
BioPearl Microspheres consist of hydrogel microspheres capable of resorption over time after implantation in the arteries. BioPearl Microspheres are hydrophilic, precisely calibrated, biocompatible, and capable of loading and eluting chemotherapeutic agents (such as Doxorubicin, Epirubicin, and Idarubicin) in a controlled manner. The degradation profile of BioPearl Microspheres is designed such that there is an opportunity for progressive restoration of blood flow to the target implant site.

BioPearl Microspheres are available in the following sizes:

Size Offering	Size Range of Microspheres*
BP200	100-350 µm

*At least 90% of the microspheres can be expected to fall within the listed size range 10-15 minutes after reconstitution.

Qualitative and Quantitative Materials Information	
Substance and/or Material	**Limits**
Dimethylacrylamide	≤ 20 ppm
Glycerol monomethacrylate	≤ 20 ppm
3-Sulfopropyl acrylate potassium salt	≤ 20 ppm
Biodegradable Crosslinker	≤ 20 ppm

PACKAGING:
- BioPearl Microspheres are provided in a sterile 10 ml glass vial containing dry microspheres that have an equivalent volume of approximately 2 ml of product once reconstituted in physiological buffered saline.
- The vial of sterile BioPearl Microspheres is sealed with a rubber septum and an aluminum flip-tear cap.

INTENDED PURPOSE:
BioPearl Microspheres are indicated for embolization of blood vessels supplying hypervascular primary tumors or metastases in the liver.

Note: BioPearl Microspheres can be loaded with chemotherapeutic drugs. The BioPearl Microspheres are compatible with Doxorubicin, Epirubicin, and Idarubicin, which can be loaded prior to embolization and then, as a secondary action, elute a local, controlled, and sustained dose to the tumor after embolization. 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.

CONTRAINDICATIONS:
1. Targeted embolization of blood vessels belonging to the central vascular system (pulmonary arteries, ascending aorta, aortic arch, descending aorta to the aortic bifurcation, coronary arteries, common carotid artery, external carotid artery, internal carotid artery, cerebral arteries, brachiocephalic artery, cardiac veins, pulmonary veins, superior vena cava, inferior vena cava)
2. Patients intolerant to vascular occlusion procedures
3. Vascular anatomy or blood flow that precludes catheter placement or embolic agent injection
4. Presence or likely onset of vasospasm or hemorrhage
5. Presence of severe atheromatous disease

6. Presence of collateral vessel pathways potentially endangering normal territories during embolization
7. Presence of arteries supplying the lesion not large enough to accept BioPearl Microspheres
8. Vascular resistance peripheral to the feeding arteries precluding passage of BioPearl Microspheres into the lesion
9. Patient is pregnant
10. Patient has known allergies to radio-opaque contrast agent, drugs and their additives
11. Do not use BioPearl Microspheres in the following applications:
    a. Embolization 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)
    b. Any vasculature where BioPearl Microspheres could pass directly into non-target territories

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

- Undesirable reflux or passage of BioPearl Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries/arterial beds or veins.
- Non-target embolization.
- Pulmonary embolization.
- Ischemia at an undesirable location, including ischemic stroke or ischemic infarction.
- Capillary bed saturation and tissue damage.
- 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 arterial access site.
- Deep vein thrombosis or clotting of a deep vein in a patient's leg.
- Thrombosis of the artery at the arterial access site.
- 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 BioPearl Microspheres in conjunction with embolization devices based on organic solvents such as ethyl alcohol and dimethyl sulfoxide (DMSO) at the same embolization site.

CAUTIONS:

- Do not use if the vial, septum, or aluminum cap appears damaged.
- BioPearl Microspheres MUST NOT be used in their original dry state. They must be reconstituted before use. See the "Device Preparation" section for reconstitution steps.
- Embolization with BioPearl Microspheres should only be performed by a physician with appropriate interventional training.
- Each package of BioPearl Microspheres is intended for single patient use only. Discard any unused material**.** Do not re-sterilize.
- The physician should carefully select the size and the quantity of the BioPearl Microspheres according to the lesion to be treated, based on the physician's education, training and currently available scientific evidence.
- Physicians must decide the appropriate time to stop the infusion of BioPearl Microspheres.

- Proximal slowing and termination of flow may indicate that the vessel or the target area is occluded. Careful fluoroscopic monitoring is required.
- Microsphere embolization must be performed slowly. The injection speed and manner must be controlled. Excessive injection rate may result in retrograde flow in the vessel leading to non-targeted embolization of healthy tissue or organs.
- Do not use BioPearl Microspheres that have been improperly stored or mishandled.
- If arteriovenous anastomoses, branch vessels which lead away from the targeted embolization area, or emergent vessels not evident prior to embolization are present, they can lead to non-targeted embolization and cause severe complications for the patient.
- Particles smaller than 100 µm can migrate to distal anastomotic feeders and embolize circulation to distal tissue. For this reason, smaller particles have a greater likelihood of causing unwanted ischemic injury. This should be considered prior to starting the embolization procedure. Possible consequences include, but are not limited to, paralysis, necrosis, swelling, abscess information and severe post-embolization syndrome.
- Ischemia of tissue adjacent to the target area may result from post-embolization swelling. Therefore, special care should be taken to avoid such ischemia of non-tolerant, non-targeted tissue such as a nervous system.
- If there are any symptoms of unwanted embolization during injection, consider stopping the procedure to evaluate the possibility of shunting. Such symptoms may include changes in patient's vital signs, such as hypoxia or central nervous system changes.

INTERACTIONS WITH PHARMACEUTICALS:

- There are no known chemical interactions between BioPearl Microspheres and pharmaceuticals.

IN VIVO STUDIES:

- *In vivo* testing of this device based on histological evaluation has demonstrated degradation beginning as early as 1 day, with partial degradation of microspheres at 4 weeks in an animal model. At 12 weeks, BioPearl Microspheres have been observed at various stages of degradation.
- *In vivo* testing of this device based on fluoroscopic evaluation has shown an increased flow to the target site as early as 2 weeks following implantation after embolization with approximately 1 ml of BioPearl Microspheres in an animal model.

**Note: The data from animal studies may not reflect human use outcome.*

DRUG SELECTION AND LOADING:

The BioPearl Microspheres are compatible with Doxorubicin, Epirubicin, and Idarubicin, which can be loaded prior to embolization and then, as a secondary action, elute a local, controlled, and sustained dose to the tumor after embolization. For drug loading, please refer to the included loading instructions.

DEVICE PREPARATION:

The BioPearl Microspheres must be rehydrated prior to use. Degradation is a continuous process that begins when the BioPearl Microspheres are exposed to aqueous media. Do not rehydrate the BioPearl Microspheres until it is confirmed that the microspheres will be used within the stability period as listed in the included loading instructions.

1. Select an appropriately-sized syringe for the volume of drug to be added.
    a. Doxorubicin Powder: Use a 20 ml syringe or larger.
    b. Doxorubicin Liquid: Use a 50 ml syringe or larger.
    c. Epirubicin: Use a 50 ml syringe or larger.
    d. Idarubicin: Use a 20 ml syringe or larger.
2. Fill the user-supplied syringe with 5-10 ml of physiological buffered saline or saline.
3. Connect the syringe to a needle of 20-gauge diameter or larger.
4. Carefully insert the needle of the syringe through the stopper of the vial. Take care not to core the rubber stopper.

5. Inject the fluid from the syringe. Proper aspiration and/or venting techniques, as approved by the healthcare facility, may be used for easier injection of reconstitution medium into the vial. Prior to injecting the reconstitution fluid, it may be necessary to manually aspirate air from the vial into the syringe.
6. Remove the needle and syringe. Shake the vial so that the liquid contacts the stopper at least 10 times.
7. Wait a minimum of 10 minutes and no longer than 15 minutes to allow the BioPearl Microspheres to reconstitute and expand to their intended size.
8. Gently shake the vial to make the contents homogenous and use the user-provided syringe and needle to gently aspirate the entire contents of the vial into the syringe. If 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. Take care not to core the rubber stopper.

INSTRUCTIONS FOR USE:

- Prior to the embolization procedure, evaluate the vascular anatomy associated with the lesion using high resolution angiographic imaging.
- BioPearl Microspheres are designed to be used in a variety of micro-catheters and catheters.
- Select a delivery catheter of appropriate size, suitable for the dimensions of target vessels.
- Utilize catheter's minimum inner diameter measurement to determine the catheter compatibility with the microspheres.

Microcatheter Compatibility Chart	
Size Offering	Microcatheter
BP200	≥ 0.021" ID

- Care should be taken to choose the appropriate size of BioPearl Microspheres that best matches the pathology (i.e. vascular target/vessel size) and provides the desired clinical outcome.
- Introduce the delivery catheter into the target vessel according to standard techniques. Position the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels.
- BioPearl Microspheres are not radio-opaque. It is recommended to monitor the embolization under fluoroscopic visualization by adding the desired amount of contrast medium to the suspension fluid. See the included loading instructions for the recommended contrast medium ratio.
- Take care to ensure proper suspension of the BioPearl Microspheres in the contrast medium to optimize distribution during injection.
- Slowly inject BioPearl Microspheres into the delivery catheter under fluoroscopic visualization while observing the contrast flow rate. Exercise conservative judgment in determining the embolization endpoint.
- Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge BioPearl Microspheres still within the catheter lumen.
- Discard any unused BioPearl Microspheres.

MRI SAFETY INFORMATION

MR

The BioPearl Microspheres for embolization is **MR Safe** (i.e., an item that poses no known hazards in all MR environments).

STORAGE AND HANDLING:

- Avoid exposure to water, sunlight, extreme temperatures, and high humidity during storage. Store unopened BioPearl Microspheres under controlled room temperature.
- Use by the date indicated on the vial/carton label.
- Do not freeze.

SUMMARY OF SAFETY AND CLINICAL PERFORMANCE:

- The Summary of Safety and Clinical Performance (SSCP) for the device will be accessible in the European Database on Medical Devices (EUDAMED) after the launch of the EUDAMED database (https://ec.europa.eu/tools/eudamed). The SSCP will be linked to the Basic UDI-DI (08402732BIOPEARLM7) in the EUDAMED. A patient implant card is included in the package. This card should be completed and provided to the patient.
- Additional product information is available at the MicroVention website (www.microvention.com/emea/peripheral-products/product-use-and-safety).

SYMBOLS:

	Contents
	Catalog number
	Batch code
	Country and date of manufacture
	Manufacturer
	Use-by date
	CE Mark with Notified Body Reference #
	Sterilized using irradiation
	Keep dry
	Consult instructions for use
	Do not reuse
	Keep away from sunlight
	Non-pyrogenic

	Do not use if package is damaged
	Caution
EC REP	Authorized European Representative
MD	Medical device
	Distributor
UDI	Unique device identifier
	Single sterile barrier system
	Importer
MR	MR Safe

WARRANTY:
MicroVention warrants that reasonable care has been used in the design and manufacture of this device. This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether expressed or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for particular purpose. Handling, storage, cleaning and sterilization of the device as well as factors relating to the patient, diagnosis, treatment, surgical procedure and other matters beyond MicroVention's control directly affect the device and the results obtained from its use. MicroVention's sole obligation under this warranty is limited to the repair or replacement of this device through its expiration date, and MicroVention shall not be liable for any incidental, indirect, special or consequential loss, damage or expense directly or indirectly arising from the use of this device. MicroVention neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this device. MicroVention assumes no liability with respect to devices reused, reprocessed or re-sterilized and makes no warranties, expressed or implied, including, but not limited to, merchantability or fitness for intended use, with respect to such device.

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