What are the indications for HepaSphere Microspheres?

• HepaSphere Microspheres are CE marked and 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.
Are HepaSphere Microspheres approved by the FDA?

- HepaSphere Microspheres are not currently available for sale or distribution in the United States.
Can HepaSphere Microspheres load fluorouracil?

• 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 are not indicated for use with fluorouracil.
Can HepaSphere Microspheres load epirubicin?

• 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 are not indicated for use with epirubicin.
Can HepaSphere Microspheres load cisplatin/oxaliplatin?

• 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 are not indicated for use with platins.
HepaSphere Microspheres are packaged in a 10 mL glass vial.

- The vial has a vacuum.
- Each vial contains 25 mg of HepaSphere Microspheres.
- The vial is stopper-sealed by an aluminum cap equipped with a color-coded lid.
- Each vial is single-use only.
- The vial should not be re-sterilized and any unused material should be properly discarded.
HepaSphere Microspheres come in what size ranges?

<table>
<thead>
<tr>
<th>Label Color</th>
<th>Sphere Size (Dry)</th>
<th>Sphere Size (Hydrated in 0.9% NaCl or Non-Ionic Contrast Media)</th>
<th>Dosage of Spheres</th>
<th>Catalog Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange</td>
<td>30-60 μm</td>
<td>120-240 μm</td>
<td>25 mg</td>
<td>V225HS</td>
</tr>
<tr>
<td>Yellow</td>
<td>50-100 μm</td>
<td>200-400 μm</td>
<td>25 mg</td>
<td>V325HS</td>
</tr>
<tr>
<td>Blue</td>
<td>100-150 μm</td>
<td>400-600 μm</td>
<td>25 mg</td>
<td>V525HS</td>
</tr>
<tr>
<td>Red</td>
<td>150-200 μm</td>
<td>600-800 μm</td>
<td>25 mg</td>
<td>V725HS</td>
</tr>
</tbody>
</table>

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How many microspheres are there per vial of HepaSphere Microspheres?

<table>
<thead>
<tr>
<th>Sphere Size (Dry)</th>
<th>Sphere Size (Hydrated)</th>
<th>Number of Spheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-60 μm</td>
<td>120-240 μm</td>
<td>815,000</td>
</tr>
<tr>
<td>50-100 μm</td>
<td>200-400 μm</td>
<td>139,000</td>
</tr>
<tr>
<td>100-150 μm</td>
<td>400-600 μm</td>
<td>28,100</td>
</tr>
<tr>
<td>150-200 μm</td>
<td>600-800 μm</td>
<td>9,400</td>
</tr>
</tbody>
</table>

*Calculation based on the mean diameters of microspheres and weight/volume ratio. Data on file at Biosphere® Medical.
Why are HepaSphere Microspheres packaged dry?

• HepaSphere Microspheres are packaged dry because this allows for loading of aqueous-based solutions mechanically.

• HepaSphere Microspheres also have a negative charge that ionically attracts the positive charge of doxorubicin.

• In original packaging, HepaSphere Microspheres have a 36-month shelf life.
How do I reconstitute HepaSphere Microspheres?

- Use 0.9% saline or non-ionic contrast medium.
- NEVER USE PURE WATER TO RECONSTITUTE HEPASPHHERE MICROSPHERES OR TO RECONSTITUTE DOXORUBICIN WITH HEPASPHHERE MICROSPHERES.
- Please refer to the package insert for reconstitution instructions.
How do HepaSphere Microspheres load doxorubicin?

There are 2 mechanisms of loading

• **Ionic:** The doxorubicin is loaded into HepaSphere Microspheres and eluted by a “reversible ionic exchange mechanism.”
  – The negatively charged HepaSphere Microspheres interact with the protonated (positive) amine of the doxorubicin hydrochloride.

• **Mechanical:** HepaSphere Microspheres mechanically absorb aqueous-based solutions whether or not they are positively charged.

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What is doxorubicin?

- Doxorubicin is indicated for the treatment of several cancers, including bladder, breast, leukemia (some types), liver, lung, lymphomas, mesothelioma, multiple myeloma, neuroblastoma, and uterine.
- Doxorubicin is an anti-cancer chemotherapy drug.
- Doxorubicin is classified as an anthracycline antibiotic.
- Chemotherapy drugs work by damaging the RNA or DNA that tells the cell how to copy itself in division.
- If the cells are unable to divide, they die.
What is the loading protocol for HepaSphere Microspheres with doxorubicin?

- There are two loading protocols for HepaSphere Microspheres: powdered doxorubicin and pre-solubilized doxorubicin.
- Please refer to the IFU and mixing charts for loading instructions.
How long does it take to load HepaSphere Microspheres with doxorubicin?

• Please refer to the IFU and mixing charts for more information.

<table>
<thead>
<tr>
<th>Type of Doxorubicin</th>
<th>Loading Time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powdered Doxorubicin (5 mg/mL reconstituted from powder)</td>
<td>60 minutes</td>
</tr>
<tr>
<td>Pre-solubilized Doxorubicin</td>
<td>120 minutes</td>
</tr>
</tbody>
</table>

*Loading time for 50 mg or 75 mg of doxorubicin
How much doxorubicin can be loaded in a vial of HepaSphere Microspheres?

- The maximum amount of doxorubicin that can be loaded into a vial of HepaSphere Microspheres is 75 mg.
What is the appearance of HepaSphere Microspheres during and following loading with doxorubicin?

• When loading HepaSphere Microspheres with doxorubicin, the sphere color changes to dark red.
• Please note that after the required loading time, the solution may retain some red coloration. This is normal. It is not an indication that HepaSphere Microspheres failed to load.

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What type of contrast should I use with HepaSphere Microspheres?

- Always use non-ionic contrast medium.
Can I use Lipiodol®?

• When using HepaSphere Microspheres, you do not need to add Lipiodol.
Are there any peer-reviewed publications for HepaSphere Microspheres?

- For a comprehensive list of peer-reviewed publications, please refer to our bibliography. Below are some key publications regarding HepaSphere Microspheres.

- **Peer-reviewed Clinical Data**

- **Animal Data**

- **In Vitro Data**

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