HepaSphere™ MICROSPHERES

English

INSTRUCTIONS FOR USE

INTENDED USE

HepaSphere™ Microspheres are indicated for use in embolisation of blood vessels with or without delivery of doxorubicin HCl for therapeutic or preoperative purposes in the following procedures:

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

DESCRIPTION

HepaSphere Microspheres are part of a family of embolic agents based on proprietary technologies. They are designed for controlled, targeted embolisation. The HepaSphere Microspheres can be loaded with doxorubicin HCl and are able to release the drug locally at the embolisation site. 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)	30-60	50-100	100-150	150-200

DEVICE PACKAGING

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

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 embolisation
- 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 to prevent passage from any 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 misembolisation, 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 embolisation 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 mistargeted embolisation. 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 mistargeting occur or patient symptoms develop.
- Consider upsizing the microspheres if angiographic evidence of embolisation 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 embolisation can lead to mistargeted embolisation and severe complications.
- Microspheres smaller than 100 microns will generally migrate distal to anastomotic feeders and therefore are more likely to terminate circulation to distal tissue. Greater potential of ischaemic injury results from use of smaller sized microspheres and consideration must be given to the consequence of this injury prior to embolisation. The potential consequences include swelling, necrosis, paralysis, abscess and/or stronger post-embolisation syndrome.
- Post embolisation swelling may result in ischaemia to tissue adjacent to target area. Care must be given to avoid ischaemia of intolerant, non targeted tissue such as nervous tissue.

PRECAUTIONS

HepaSphere Microspheres must only be used by physicians trained in vascular embolisation 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 resterilise the contents of a vial that has been opened. Reusing, reprocessing or resterilising 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 resterilising 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. The microspheres swell to approximately four times their diameter in 0.9% NaCl aqueous solution and non-ionic contrast media, as compared to their initial dry diameter. The magnitude of swelling when loaded with doxorubicin HCl is dependent upon the amount of drug with which the product is loaded.

Lyophilized doxorubicin HCl must be reconstituted in NaCl 0.9% solution.

HepaSphere Microspheres undergo a size decrease of about 20% when loaded with doxorubicin HCl compared to the size in pure NaCl 0.9% aqueous solution. 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 embolisation target and possible embolisation 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. Patients with known allergies to non-ionic contrast media may require corticosteroids prior to embolisation.

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, refer to the appropriate drug IFU for information concerning contraindications, warnings, precautions, potential complications, dosage and patient management before use.

POTENTIAL COMPLICATIONS

Vascular embolisation 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:

- Paralysis resulting from untargeted embolisation or ischaemic injury from adjacent tissue oedema
- 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
- Ischaemia at an undesired location, including ischaemic stroke, ischaemic infarction (including myocardial infarction), and tissue necrosis
- Capillary bed occlusion and tissue damage
- Vasospasm
- Recanalisation
- Blindness, hearing loss, and loss of smell
- Foreign body reactions necessitating medical intervention
- Infection necessitating medical intervention
- Complications related to catheterisation (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)
- Allergic reaction to medications (e.g. analgesics)
- Allergic reaction to non-ionic contrast media or embolic material
- Vessel or lesion rupture and haemorrhage
- 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 non-ionic contrast medium, or 50% nonionic contrast and 50% NaCl 0.9% aqueous solution, HepaSphere Microspheres swell approximately four 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.

Note: To expand properly, HepaSphere Microspheres need to be exposed to a minimum of 10 mL solution.

The magnitude of swelling when loaded with doxorubicin HCl is dependent upon the amount of drug with which the product is loaded. HepaSphere Microspheres undergo a size decrease of about 20% when loaded with doxorubicin HCl compared to the size in pure NaCl 0.9% aqueous solution.

CATHETER COMPATIBILITY

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

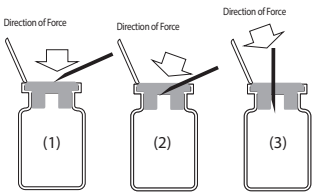
Dry (µm)	Approximate Reconstituted Size range (µm)	Catheter Size ID (in.)
30-60	120 - 240	≥ 0.021
50-100	200 - 400	≥ 0.021
100-150	400 - 600	≥ 0.024
150-200	600 - 800	≥ 0.027

INSTRUCTIONS

HepaSphere Microspheres must be reconstituted with 100% NaCl 0.9% aqueous solution or non-ionic contrast medium, or 50% non-ionic contrast medium and 50% NaCl 0.9% aqueous solution if using without delivery of doxorubicin HCl, or loaded with doxorubicin HCl solution 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".

- HepaSphere Microspheres may be present outside the vial. Therefore, the vial must be aseptically handled away from the main sterile field.
- 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. Remove the vial from the pouch. The external surface of the vial is sterile.
- To prevent coring the rubber stopper, insert the injection needle as follows:
  (1) Hold the needle so that the cutting edge faces upwards and position the tip diagonally to the insertion site. Press the tip against the center of the insertion site.
  (2) Apply a gentle force to the needle in the opposite direction to the cutting edge 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 cutting edge, 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.

HEPASPHERE MICROSPHERES CAN BE USED WITH OR WITHOUT LOADING OF DOXORUBICIN HCl.

OPTION 1: PREPARATION FOR Embolisation WITHOUT DOXORUBICIN HCl (BLAND)

The approximate reconstitution time when used without loading of doxorubicin HCl is 10 minutes.

- Fill a 10 mL syringe with 100% NaCl 0.9% aqueous solution or nonionic contrast medium (or 50% NaCl 0.9% aqueous solution and 50% contrast). 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 (10 mL) 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, gently invert the vial back and forth so that the liquid contacts the stopper 5-10 times.

Note: Vigorous shaking may introduce micro bubbles, which can cause the microspheres to aggregate.

- Wait a minimum of 10 minutes to allow the HepaSphere Microspheres to reconstitute and expand fully.
- Use a 30 mL 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. Gently aspirate the entire contents of the vial into the syringe.

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.

Note: HepaSphere Microspheres reconstituted as described above can be used in the presence of chemotherapeutic agents such as cisplatin, epirubicin, doxorubicin HCl, fluorouracil, irinotecan and mitomycin after hydration. However for drug delivery, HepaSphere Microspheres are only indicated for use with doxorubicin HCl (see below Option 2).

- If microspheres were reconstituted using 100% NaCl 0.9%, nonionic contrast medium must be added to the syringe containing the HepaSphere Microspheres for visualisation under fluoroscopy. If nonionic contrast medium was used to reconstitute the microspheres, additional non-ionic contrast medium may be added.

OPTION 2: PREPARATION FOR Embolisation LOADED WITH DOXORUBICIN HCl

WARNING: Liposomal formulations of doxorubicin HCl are not suitable for loading into HepaSphere Microspheres.

As a general guideline, the loading of lyophilised doxorubicin HCl solubilised in NaCl 0.9% solution into HepaSphere Microspheres will take one hour.

The HepaSphere Microspheres should not be used before they are fully hydrated and expanded. Loading kinetics of pre-solubilised doxorubicin HCl may vary, depending on the concentration and pH of the solution.

- Choose the appropriate dose of doxorubicin HCl to load into the HepaSphere Microspheres.

Note:A maximum dose of doxorubicin HCl **75 mg** can be loaded into each vial of HepaSphere Microspheres. Solubilize the desired dose of lyophilised doxorubicin HCl in 20 mL of NaCl 0.9% solution for injection. NEVER USE PURE WATER.

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.

- Aspirate the 20 mL of doxorubicin HCl solution into two separate 30 mL syringes. Each 30 mL syringe should contain 10 mL of doxorubicin HCl solution.
- Connect one of the 30 mL syringes containing 10 mL of the doxorubicin HCl solution to a needle of 20 gauge diameter or larger.
- To ensure proper reconstitution of the HepaSphere Microspheres, grasp the HepaSphere Microspheres 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 of one of the 30 mL syringes containing 10 mL of doxorubicin HCl solution through the stopper of the vial. Continue rolling the vial in your fingertips and inject the full 10mL of doxorubicin HCl solution into the vial.
- Place the HepaSphere Microspheres vial vertically. Carefully remove the syringe with the needle attached, and allow the vial to stand for 10 minutes in order to completely hydrate the spheres.
- During the 10 minute hydration period, shake the HepaSphere Microspheres vial several times back and forth so that the liquid contacts the grey stopper. Repeat this process every 2-3 minutes to ensure a homogenous reconstitution of the HepaSphere Microspheres.

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 media into the vial. If aspiration of air from the vial is performed prior to reconstitution, exercise caution not to remove the spheres from the vial.

- After the 10 minute hydration period, attach a 20 gauge or larger needle to the second 30 mL syringe containing the remaining 10 mL of doxorubicin HCl solution and insert into the HepaSphere Microspheres vial. Aspirate the contents of the HepaSphere Microspheres vial into the 30mL syringe containing the remaining 10 mL of doxorubicin HCl solution. 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. Gently aspirate the entire contents of the vial into the syringe.
- Prior to removing the needle from the HepaSphere Microspheres vial, while holding the syringe vertically, gently pull the plunger of the syringe down, removing any solution that may be in the hub of the needle.
- Replace the needle with a syringe cap and invert the syringe back and forth to disperse the contents within the syringe. Wait a minimum of 60 minutes to allow the HepaSphere Microspheres to expand fully and load the doxorubicin HCl. During the 60 minutes, the syringe should be inverted every 10 – 15 minutes in order to optimize the drug distribution into the spheres.
- After 60 minutes, let the syringe stand for the spheres to settle down and purge all supernatant and discard it following facility approved standards.
- Add a minimum of 20 mL of non-ionic contrast medium to the 30 mL syringe containing the doxorubicin HCl loaded HepaSphere Microspheres, however larger volume of solution can provide better control during embolisation. Gently invert the syringe 2 or 3 times and wait 5 min until solution homogeneity is reached.
- Before any injection, check the spheres are in suspension, if not invert the syringe back and forth to disperse contents within the syringe.

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 embolisation.

- Using standard techniques, position the delivery catheter within the target vessel and the catheter tip as close as possible to the embolisation target.
- Use an injection syringe no larger than 3mL for the delivery of doxorubicin loaded HepaSphere Microspheres. Use of a 1 mL injection syringe is recommended.
- Aspirate the HepaSphere Microspheres mixture into the injection syringe.
- Two methods for embolic aliquot sequestering for injectionmay be used:

  - Option 1: Connect a 3 way-stopcock to the 30 mL syringe containing the doxorubicin loaded HepaSphere Microspheres 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 the doxorubicin loaded HepaSphere Microspheres can be drawn from the 30 mL syringe into a 1 mL injection syringe through a 3 way-stop cock that is not attached to the infusion catheter. The 1 mL syringe containing each aliquot can be attached independently to the infusion microcatheter and injected.
- Invert the 30 mL syringe back and forth to maintain the homogenous suspension of the HepaSphere Microspheres mixture.
- Under continuous fluoroscopic guidance, inject the aliquot of doxorubicin loaded 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 ischaemia of untargeted tissues and vessels.

- When stasis in the feeding pedicle occurs while delivering the doxorubicin HCl loaded 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 devascularisation 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 embolisation. Remove the catheter while applying gentle aspiration and discard.

CONSERVATION AND STORAGE

HepaSphere Microspheres must be stored in a dry, dark place in their original vials and packaging. Use by the date indicated on the labelling.

When the procedure of reconstitution is completed, store the solution of HepaSphere Microspheres in 2°C to 8°C conditions and use within 24 hours, **IF** not used immediately. Do not store HepaSphere Microspheres after contrast medium has been added.

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

Information on packaging:

Symbole	Designation
	Manufacturer: Name & Address
	Use by date: year-month-day
LOT	Batch code
REF	Catalogue number
	Do not resterilise
	Do not use if package is damaged
	Keep away from sunlight
	Keep dry
	Do not re-use
	Caution - Refer to Instructions For Use
	Non-pyrogenic
STERILE R	Sterilised using irradiation
CE	EC mark logo - Notified body identification : 0459
	Size of dry microspheres / Size of hydrated microspheres

All serious or life threatening adverse events or deaths associated with use of HepaSphere Microspheres should be reported to the device manufacturer.

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