

DC BEAD™

DC BEAD^{M1}™

HEP ASPHERE™

LIFEPEARL™

TANDEM™

DRUG-ELUTING BEADS CURRENT INDICATION STATUS

DCBead™

DCBead^{M1}™

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BTG

DC BEAD™ INDICATIONS

DCBead™

DC BEAD™

DC BEAD™

HEPASPHERE™

LIFEPEARL™

TANDEM™

The CE Mark approved indication statements for DC Bead™ include loading with doxorubicin and with irinotecan.

INDICATIONS:

DC Bead are intended to be loaded with doxorubicin for the purpose of:

- Embolisation of vessels supplying malignant hypervascularised tumour(s).
- Delivery of a local, controlled, sustained dose of doxorubicin to the tumour(s).

INDICATIONS:

DC Bead are intended to be loaded with irinotecan for the purpose of:

- Embolisation of vessels supplying malignant colorectal cancer metastasised to the liver (mCRC)
- Delivery of a local, controlled, sustained dose of irinotecan to the mCRC.

Full DC Bead™ IFU on pages 3 to 7

Doxorubicin: page 3

Irinotecan: page 6

Indicated for loading with doxorubicin ✓

Indicated for loading with irinotecan ✓

DC Bead™ instructions for use CN00103.5 and CN000164.2

**INSTRUCTIONS FOR USE****DC Bead™ Drug Delivery Embolisation System****STERILE • SINGLE USE ONLY • NON-PYROGENIC****DESCRIPTION:**

DC Bead comprise a range of hydrogel microspheres that are biocompatible, hydrophilic, non resorbable, precisely calibrated and capable of loading doxorubicin. DC Bead is produced from polyvinyl alcohol and are available in the following size ranges:

Nominal Bead Size	Label Colour	<i>Upon loading with doxorubicin, DC Bead undergo a slight decrease in size, up to 20% when loading at 25mg/mL.</i>
100 – 300 µm	Yellow	
300 – 500 µm	Blue	
500 – 700 µm	Red	
700 – 900 µm	Green	

PRESENTATION:

- 10 ml glass vial
- Each vial contains approximately 2 ml of DC Bead in non-pyrogenic, sterile, physiological buffered saline. Total volume of saline and DC Bead is approximately 8ml.
- The vial is stopper sealed by an aluminium cap equipped with a colour-coded lid.
- Each vial is intended for single patient use only. Do not resterilise. Discard any unused material.

INDICATIONS:

DC Bead are intended to be loaded with doxorubicin for the purpose of:

- Embolisation of vessels supplying malignant hypervascularised tumour(s).
- Delivery of a local, controlled, sustained dose of doxorubicin to the tumour(s).

CONTRAINDICATIONS – DC BEAD:

- Patients intolerant to vascular occlusion procedures.
- Vascular anatomy that precludes catheter placement or emboli injection.
- Presence or likely onset of vasospasm.
- Presence or likely onset of haemorrhage.
- Presence of severe atheromatous disease.
- Presence of feeding arteries smaller than distal branches from which they emerge.
- Presence of patent extra-to-intracranial anastomoses or shunts.
- Presence of collateral vessel pathways potentially endangering normal territories during embolisation.
- Presence of end arteries leading directly to cranial nerves.
- Presence of arteries supplying the lesion not large enough to accept DC Bead.
- Vascular resistance peripheral to the feeding arteries precluding passage of DC Bead into the lesion.
- Do not use DC Bead in the following applications:
 - i. Embolisation of non-malignant tumours.
 - ii. Embolisation of large diameter arteriovenous shunts (ie. where the blood does not pass through the arterial/capillary/venous transition but directly from artery to vein)
 - iii. Any vasculature where DC Bead Embolic Agent could pass directly into the internal carotid artery or other non-target territories.

CONTRAINDICATIONS – DOXORUBICIN:

- See doxorubicin package insert for contraindications regarding use.

WARNING: Studies have shown that DC Bead do not form aggregates and, as a result, penetrate deeper into the vasculature as compared to similarly sized PVA particles.

**CAUTIONS:**

- Do not use if the vial or packaging appear damaged.
- Select the size and quantity of DC Bead appropriate for the pathology to be treated.
- Embolisation with DC Bead should only be performed by a physician with appropriate interventional occlusion training in the region intended to be embolised.
- **Exceeding a loading dose of 37.5mg doxorubicin per 1ml DC Bead may lead to some systemic distribution of doxorubicin and related side effects.**

POTENTIAL COMPLICATIONS:

- Undesirable reflux or passage of DC Bead into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
- Non-target embolisation.
- Pulmonary embolisation.
- Ischaemia at an undesirable location.
- Capillary bed saturation and tissue damage.
- Ischaemic stroke or ischaemic infarction.
- Vessel or lesion rupture and haemorrhage.
- Neurological deficits including cranial nerve palsies.
- Vasospasm.
- Death.
- Recanalisation.
- Foreign body reactions necessitating medical intervention.
- Infection necessitating medical intervention.
- Clot formation at the tip of the catheter and subsequent dislodgement.

DRUG LOADING INSTRUCTIONS:

DC Bead is suitable for loading doxorubicin-HCl ONLY. Liposomal formulations of doxorubicin are not suitable for loading into DC Bead.

To obtain a final loading of 50mg doxorubicin per 2ml vial of DC Bead:

- Reconstitute a vial containing 50mg of doxorubicin with 2ml of sterile water for injection. Mix well to obtain a clear red solution (25mg/ml).
- Remove as much saline as possible from a vial of DC Bead using a syringe with a small gauge needle.
- Using a syringe and needle add the 2ml of reconstituted doxorubicin solution directly to the vial of DC Bead.
- Agitate the DC Bead/doxorubicin solution occasionally to encourage mixing until the DC Bead is red. Although the solution retains a red colour, the doxorubicin will be loaded.
- Loading will take a minimum of 20 minutes for the smallest size DC Bead and up to 120 minutes for the largest size DC Bead.
- Prior to use, transfer the DC Bead loaded with doxorubicin to a syringe and add an equal volume of non-ionic contrast media. Invert the syringe gently to obtain an even suspension of DC Bead.
- A dose of up to 37.5mg doxorubicin per ml DC Bead can be loaded.
- viii. The maximum recommended total dose of doxorubicin per procedure is 150mg.**

STORAGE OF DRUG LOADED DC BEAD:

- In order to minimise the risk of microbiological contamination DC Bead should be prepared under controlled aseptic conditions. As the preparation and loading conditions of DC Bead are outside of the manufacturers' control, once the DC Bead vial has been pierced, the allocation of a shelf life longer than 4 hours if used at room temperature or 24 hours if stored in a refrigerator at 2-8°C is the responsibility of the user. DC Bead loaded with doxorubicin is physically and chemically stable for 14 days if stored in a refrigerator at 2-8°C and 7 days if mixed with non-ionic contrast media and stored in a refrigerator at 2-8°C.

**DELIVERY INSTRUCTIONS:**

- Carefully evaluate the vascular network associated with the lesion using high resolution imaging prior to beginning the embolisation procedure.
- DC Bead are available in a range of sizes. Care should be taken to choose the appropriate size of DC Bead that best matches the pathology (ie. vascular target/vessel size) and provides the desired clinical outcome.
- Choose a delivery catheter based on the size of the target vessel. DC Bead can tolerate temporary compression of 20% to 30% in order to facilitate passage through the delivery catheter.
- 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.
- DC Bead are not radio-opaque. It is recommended to monitor the embolisation under fluoroscopic visualization by adding the desired amount of contrast medium to the suspension fluid.
 - Take care to ensure proper suspension of the DC Bead in the contrast medium to enhance distribution during injection.
 - Draw the DC Bead into a syringe needle of a size greater than or equal to 19 gauge (1.07 mm).
 - Slowly inject DC Bead into the delivery catheter under fluoroscopic visualization while observing the contrast flow rate. Exercise conservative judgment in determining the embolisation endpoint.
- Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge DC Bead still within the catheter lumen.
- Discard any unused DC Bead loaded with doxorubicin.

CONSERVATION AND STORAGE:

- Store unopened DC Bead in a cool, dry and dark place in its original packaging.
- Use by the date indicated on the vial label.
- Do not freeze.

PACKAGE LABEL:

REF	Catalogue number	Steam Sterilised	Protect from moisture
LOT	Batch number/Lot number	Use before/Expiry	Attention see instructions for use
	Do not reuse	Protect from light	Do not freeze

**DESCRIPTION:**

Upon loading with irinotecan, DC Bead undergo a slight decrease in size, up to 30% when loading at 50mg/ml.

INDICATIONS:

DC Bead are intended to be loaded with irinotecan for the purpose of:

- Embolisation of vessels supplying malignant colorectal cancer metastasised to the liver (mCRC)
- Delivery of a local, controlled, sustained dose of irinotecan to the mCRC.

CONTRAINDICATIONS – IRINOTECAN:

See irinotecan package insert for contraindications regarding use.

CAUTIONS:

On addition of contrast/water mixture to loaded beads some irinotecan will be eluted. On delivery a bolus of between 10-20mg irinotecan may be delivered. Exceeding a loading dose of 50mg irinotecan per 1ml DC Bead may lead to some systemic distribution of irinotecan and related side effects. Do not use irinotecan loaded beads with contrast agents containing salts (eg. Calcium chloride)

DRUG LOADING INSTRUCTIONS:

DC Bead are suitable for loading irinotecan Solution (20mg/ml) ONLY. To obtain a final loading of 100mg irinotecan per 2ml vial of DC Bead:

- Remove as much saline as possible from a vial of DC Bead using a syringe with a small gauge needle.
- Using a syringe and needle add the 5ml of irinotecan solution directly to the vial of DC Bead.
- Agitate the DC Bead / irinotecan solution gently to encourage mixing then allow to stand. The beads will turn a turquoise colour as the loading progresses.
- Loading will take a minimum of 2hrs for all sizes of DC Bead.
- Prior to use, transfer the DC Bead loaded with irinotecan to a syringe and add an equal volume of non-ionic contrast media. Invert the syringe gently to obtain an even suspension of DC Bead.
- A dose of up to 50mg irinotecan per ml DC Bead can be loaded.
- The maximum recommended total dose of irinotecan per procedure is 200mg.

STORAGE OF DRUG LOADED DC BEAD:

In order to minimise the risk of microbiological contamination DC Bead should be prepared under controlled aseptic conditions. As the preparation and loading conditions of DC Bead are outside of the manufacturers' control, once the DC Bead vial has been pierced, the allocation of a shelf life longer than 4 hours if used at room temperature or 24 hours if stored in a refrigerator at 2-8°C is the responsibility of the user. DC Bead loaded with irinotecan is physically and chemically stable for 14 days if stored in a refrigerator at 2-8°C. Once mixed with contrast media DC Bead loaded with irinotecan must be used immediately.

DELIVERY INSTRUCTIONS:

Discard any unused DC Bead loaded with irinotecan.

**Note:**

DC Bead™ may be loaded with a drug product, to elute a local dose of drug to tumour sites after embolisation. It is the doctor's responsibility to give due consideration to the details contained in the drug product marketing authorisation in deciding which drug to load DC Bead™ with and whether loading with that drug is appropriate for the patient under his/her care. The relevant Summary of Product Characteristics (SmPC) must be consulted. The type and dose of drug should also be assessed according to the individual patient's clinical circumstances.

Warning:

- Doxorubicin or irinotecan is not authorised (licensed) for use in transarterial chemoembolisation.
- Prescribers take responsibility for prescribing the medicine and must consult the relevant published literatures including clinical guidelines and the Summary of Product Characteristics (SmPC) to make an informed decision on which chemotherapy agent can be loaded into DC Bead™/DC BeadM1™ and whether drug loading is appropriate for the patient under his/her care, taking full account of the individual's clinical circumstances. The SmPC will not provide specific information relating to this indication or route of administration.
- Use of DC Bead™/DC BeadM1™ loaded with chemotherapy agents is contraindicated in paediatric patients.

DC BEAD^{M1}™ INDICATIONS

DC Bead^{M1}™

The CE Mark approved indication statements for DC Bead^{M1}™ include loading with doxorubicin and with irinotecan.

INDICATIONS:

DC Bead^{M1} is primarily intended as an embolic agent to treat vessels supplying malignant colorectal cancer metastasised to the liver (mCRC).

DC Bead^{M1} is compatible with irinotecan, which can be loaded prior to embolisation and then, as a secondary action, elute a local, controlled and sustained dose to the mCRC after embolisation.

INDICATIONS:

DC Bead^{M1} is primarily intended as an embolic agent for the treatment of malignant hypervascularised tumour(s).

DC Bead^{M1} is compatible with doxorubicin, which can be loaded prior to embolisation and then, as a secondary action, elute a local, controlled and sustained dose to the tumour after embolisation.

Full DC Bead^{M1}™ IFU on pages 9 to 13

Irinotecan: page 9

Doxorubicin: page 12

Indicated for loading with doxorubicin ✓

Indicated for loading with irinotecan ✓

DC Bead^{M1}™ instructions for use CN00495.1 and CN00496.1

**INSTRUCTIONS FOR USE****DC BeadM1™ embolic Drug-Eluting Bead****STERILE • SINGLE USE ONLY • NON-PYROGENIC****DESCRIPTION:**

DC BeadM1 are precisely calibrated, hydrogel embolic Drug-Eluting Beads. DC BeadM1, produced from polyvinyl alcohol, are biocompatible, hydrophilic, and non resorbable.

DC BeadM1 are capable of loading and eluting irinotecan and are available in the following size:

Label Colour	Black and Yellow
Nominal Bead Size	70 - 150µm
Loaded Bead Size	Upon loading with irinotecan, DC BeadM1 undergo a decrease in size, up to 30% when loading at 50mg/ml.

PRESENTATION:

- 10ml glass vial
- Each vial contains approximately 2ml of DC BeadM1 in non pyrogenic, sterile, physiological buffered saline. Total volume of saline and DC BeadM1 is approximately 8ml.
- The vial is stopper sealed by an aluminium cap equipped with a colour-coded lid.
- Each vial is intended for single patient use only. Do not resterilise. Discard any unused material.

INDICATIONS:

DC BeadM1 is primarily intended as an embolic agent to treat vessels supplying malignant colorectal cancer metastasised to the liver (mCRC). DC BeadM1 is compatible with irinotecan, which can be loaded prior to embolisation and then, as a secondary action, elute a local, controlled and sustained dose to the mCRC after embolisation.

CONTRAINDICATIONS – DC BeadM1:

- Patients intolerant to vascular occlusion procedures.
- Vascular anatomy that precludes catheter placement or emboli injection.
- Presence or likely onset of vasospasm.
- Presence or likely onset of haemorrhage.
- Presence of severe atheromatous disease.
- Presence of feeding arteries smaller than distal branches from which they emerge.
- Presence of patent extra-to-intracranial anastomoses or shunts.
- Presence of collateral vessel pathways potentially endangering normal territories during embolisation.
- Presence of end arteries leading directly to cranial nerves.
- Presence of arteries supplying the lesion not large enough to accept DC BeadM1.
- Vascular resistance peripheral to the feeding arteries precluding passage of DC BeadM1 into the lesion.

Do not use DC BeadM1 in the following applications:

- Embolisation of non-malignant tumours.
- Embolisation in the presence of large diameter AV shunts.
- Embolisation of arteriovenous shunts (i.e. where the blood does not pass through the arterial/capillary/venous transition but directly from artery to vein).
- Any vasculature where DC BeadM1 embolic agent could pass directly into the internal carotid artery or other non-target territories.

CONTRAINDICATIONS – IRINOTECAN:

- See irinotecan package insert for contraindications regarding use.

WARNING: Studies have shown that DC BeadM1 do not form aggregates and, as a result, penetrate deeper into the vasculature as compared to similarly sized PVA particles.

**CAUTIONS:**

- Do not use if the vial or packaging appear damaged.
- On addition of non-ionic contrast/water mixture to loaded beads some irinotecan will be eluted over time. If the beads are not used immediately, up to 10mg irinotecan may be present in the contrast/water mixture. If this occurs a small dose of irinotecan may be available systemically at time of delivery.
- Do not use irinotecan loaded beads with contrast agents containing salts (e.g. Calcium chloride)
- Ensure that DC BeadM1 is an appropriate size for the intended vasculature.
- Consider upsizing to a larger size of DC Bead in the presence of AV shunts or if angiographic evidence of embolisation does not appear quickly during delivery.
- Consideration should be given to Tc99m-MAA scanning if there is suspicion of AV shunting.
- Monitor patients carefully for signs of non-target embolisation such as hypoxia or CNS changes.
- Embolisation with DC BeadM1 should only be performed by a physician with appropriate interventional occlusion training in the region intended to be embolised.
- The maximum amount of irinotecan that can be loaded is 100mg irinotecan per 2ml vial of DC BeadM1.

Exceeding this amount may lead to some irinotecan remaining free in solution. This free solution should be removed prior to use to prevent the patient receiving the excess dose as a bolus.

POTENTIAL COMPLICATIONS:

- Undesirable reflux or passage of DC BeadM1 into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
- Non-target embolisation.
- Pulmonary embolisation.
- Ischaemia at an undesirable location.
- Capillary bed saturation and tissue damage.
- Ischaemic stroke or ischaemic infarction.
- Vessel or lesion rupture and haemorrhage.
- Neurological deficits including cranial nerve palsies.
- Vasospasm.
- Death.
- Recanalisation.
- Foreign body reactions necessitating medical intervention.
- Infection necessitating medical intervention.
- Clot formation at the tip of the catheter and subsequent dislodgement causing arterial thromboembolic sequelae.

DRUG LOADING INSTRUCTIONS:

DC BeadM1 is suitable for loading with irinotecan solution only.

A loading solution of 20mg/ml irinotecan is recommended.

To obtain a final loading of 100mg irinotecan per 2ml vial of DC BeadM1:

- i. Remove as much saline as possible from a vial of DC BeadM1 using a syringe with a small gauge needle.
- ii. Using a syringe and needle add the 5ml of irinotecan solution (20mg/ml) directly to the vial of DC BeadM1.
- iii. Agitate the DC BeadM1/irinotecan solution gently to encourage mixing, then allow to stand. Agitate the solution at intervals. The beads will turn a turquoise colour as the loading progresses.
- iv. Loading will take a minimum of 2 hours.



- v. Prior to use, transfer the DC BeadM1 loaded with irinotecan to a syringe, remove and discard any excess supernatant. Add 5ml water for injection (NOT sodium chloride) and 5-10ml of non-ionic contrast medium per ml of DC BeadM1. Mix gently to give a good suspension. Deliver suspension at a rate of 1ml per minute.
- vi. A dose of up to 100mg irinotecan per 2ml vial of DC BeadM1 can be loaded.
- vii. Up to 4ml of beads loaded with irinotecan have been documented in clinical use (Fiorentini, In vivo 21, 1085, 2007).

STORAGE OF DC BeadM1:

In order to minimise the risk of microbiological contamination DC BeadM1 should be prepared under controlled aseptic conditions. As the preparation and loading conditions of DC BeadM1 are outside of the manufacturers control, once the DC BeadM1 vial has been pierced, the allocation of a shelf life longer than 4 hours if used at room temperature or 24 hours if stored in a refrigerator at 2-8°C is the responsibility of the user. DC BeadM1 loaded with irinotecan is physically and chemically stable for 14 days if stored in a refrigerator at 2-8°C. Once mixed with contrast media DC BeadM1 loaded with irinotecan must be used immediately.

DELIVERY INSTRUCTIONS:

- Carefully evaluate the vascular network associated with the lesion using high resolution imaging prior to beginning the embolisation procedure.
- Ensure DC BeadM1 is suitable for the pathology to be treated (i.e. vascular target/vessel size).
- Choose a delivery catheter based on the size of the target vessel. DC BeadM1 can tolerate temporary compression of 20% to 30% in order to facilitate passage through the delivery catheter.
- Introduce the delivery catheter into the target vessel according to standard techniques.

- DC BeadM1 are not radio-opaque. It is recommended to monitor the embolisation under fluoroscopic visualisation by adding the desired amount of contrast medium to the suspension fluid.
- i. Take care to ensure proper suspension of the DC BeadM1 in the contrast medium to enhance distribution during injection.
- ii. Draw the DC BeadM1 into a syringe needle of a size greater than or equal to 19G (1.07mm).
- iii. Slowly inject DC BeadM1 into the delivery catheter under fluoroscopic visualisation while observing the contrast flow rate. Exercise conservative judgment in determining the embolisation endpoint.
- Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge DC BeadM1 still within the catheter lumen.
- Discard any unused DC BeadM1 loaded with irinotecan.

CONSERVATION AND STORAGE:

Store unopened DC BeadM1 in a cool, dry and dark place in its original packaging.

Use by the date indicated on the vial label.

Do not freeze.

PACKAGE LABEL:

REF	Catalogue number	Steam Sterilised	Protect from moisture
LOT	Batch number/Lot number	Use before/Expiry	Attention see instructions for use
	Do not reuse	Protect from light	Do not freeze

**DESCRIPTION:**

DC BeadM1 are capable of loading and eluting doxorubicin and are available in the following size:

Label Colour	Black and Yellow
Nominal Bead Size	70 - 150µm
Loaded Bead Size	Upon loading with doxorubicin, DC BeadM1 may undergo a decrease in diameter of 25% (the lower end of the size range being approximately 50 µm).

INDICATIONS:

DC BeadM1 is primarily intended as an embolic agent for the treatment of malignant hypervascularised tumour(s).

DC BeadM1 is compatible with doxorubicin, which can be loaded prior to embolisation and then, as a secondary action, elute a local, controlled and sustained dose to the tumour after embolisation.

CONTRAINDICATIONS – DOXORUBICIN:

- See doxorubicin package insert for contraindications regarding use.

WARNING: Studies have shown that DC BeadM1 do not form aggregates and, as a result, penetrate deeper into the vasculature as compared to similarly sized PVA particles.

CAUTIONS:

Exceeding a loading dose of 37.5mg doxorubicin per 1ml DC BeadM1 may lead to some systemic distribution of doxorubicin and related side effects.

DRUG LOADING INSTRUCTIONS:

DC BeadM1 is suitable for loading with doxorubicin-HCL ONLY. Liposomal formulations of doxorubicin are not suitable for loading into DC BeadM1. To obtain a final loading of 50mg doxorubicin per 2ml vial of DC BeadM1:

- i. Reconstitute a vial containing 50mg of doxorubicin with 2ml sterile water for injection. Mix well to obtain a clear red solution (25mg/ml).
 - ii. Remove flip cap off the vial(s) of DC BeadM1 but do not remove the metal around the bung.
 - iii. Remove as much saline as possible from a vial of DC BeadM1 using a syringe with a filter needle or small gauge needle.
 - iv. Using a syringe and needle add the 2ml of reconstituted doxorubicin solution directly to the vial of DC BeadM1.
 - v. Agitate the DC BeadM1 doxorubicin solution gently and frequently to prevent packing of the beads and encourage loading. Once the DC BeadM1 is red the doxorubicin will be loaded, although the solution may retain a red colour.
 - vi. Loading will take a minimum of 30 mins for 90% doxorubicin uptake and 60 minutes for 98% doxorubicin uptake.
 - vii. Prior to use, transfer the DC BeadM1 loaded with doxorubicin to a 20-30ml syringe using an 18 gauge needle or equivalent. Expel and discard any excess supernatant (a 5 micron needle may help with this). Add 5-10ml of non-ionic contrast medium per ml of DC BeadM1. Mix gently to give a good suspension. Deliver suspension at a rate of 1ml per minute.
 - viii. A dose of up to 37.5mg doxorubicin per 1 ml of DC BeadM1 (75mg per vial) can be loaded.
- For more detailed loading instructions see website:
www.biocompatibles.com/products/dcbead-m1/instructions-for-use.
 The maximum recommended total dose of doxorubicin per procedure is 150mg.

**STORAGE OF DC BeadM1:**

In order to minimise the risk of microbiological contamination DC BeadM1 should be prepared under controlled aseptic conditions. As the preparation and loading conditions of DC BeadM1 are outside of the manufacturers' control, once the DC BeadM1 vial has been pierced, the allocation of a shelf life longer than 4 hours if used at room temperature or 24 hours if stored in a refrigerator at 2-8°C is the responsibility of the user.

DC BeadM1 loaded with doxorubicin is physically and chemically stable for 14 days if stored in a refrigerator at 2-8°C and 7 days if mixed with non-ionic contrast media and stored in a refrigerator at 2-8°C.

Delivery Instructions:

Discard any unused DC BeadM1 loaded with doxorubicin.

Irinotecan and doxorubicin**Note:**

DC Bead™ may be loaded with a drug product, to elute a local dose of drug to tumour sites after embolisation. It is the doctor's responsibility to give due consideration to the details contained in the drug product marketing authorisation in deciding which drug to load DC Bead™ with and whether loading with that drug is appropriate for the patient under his/her care. The relevant Summary of Product Characteristics (SmPC) must be consulted. The type and dose of drug should also be assessed according to the individual patient's clinical circumstances.

Warning:

- Doxorubicin or irinotecan is not authorised (licensed) for use in transarterial chemoembolisation.
- Prescribers take responsibility for prescribing the medicine and must consult the relevant published literatures including clinical guidelines and the Summary of Product Characteristics (SmPC) to make an informed decision on which chemotherapy agent can be loaded into DC Bead™/DC BeadM1™ and whether drug loading is appropriate for the patient under his/her care, taking full account of the individual's clinical circumstances. The SmPC will not provide specific information relating to this indication or route of administration.
- Use of DC Bead™/DC BeadM1™ loaded with chemotherapy agents is contraindicated in paediatric patients.

HEPASPHERE™ INDICATIONS

The CE Mark approved indication statements for HepaSpheres™ include loading with doxorubicin and with irinotecan

INTENDED USE

HepaSpheres™ 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.

HepaSpheres Microspheres loaded with irinotecan are indicated for use in:

- Embolization of metastatic colorectal cancer (mCRC) to the liver.

Full HepaSpheres™ IFU on pages 15 to 23

HepaSpheres™ EU Instructions for Use
(730142001_001 2015-11-24) Available at:
<https://meritemea.com/wp-content/uploads/2013/11/730142001-001.pdf>
(April 2016)

Indicated for loading with doxorubicin ✓

Indicated for loading with irinotecan ✓



INSTRUCTIONS FOR USE

INTENDED USE

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.

DESCRIPTION

HepaSphere Microspheres are part of a family of embolic agents based on proprietary technologies. They are designed for controlled, targeted embolization. The HepaSphere Microspheres can be loaded with doxorubicin HCl or irinotecan, and are able to release the drug locally at the embolization 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 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.
- 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.

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.

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.

**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 nonionic 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, and 30% when loaded with irinotecan 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 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.

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:

- Paralysis resulting from untargeted embolization or ischemic 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
- Ischemia at an undesired location, including ischemic stroke, ischemic 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 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)
- Allergic reaction to medications (e.g. analgesics)
- Allergic reaction to non-ionic contrast media or embolic material
- Vessel or lesion rupture and hemorrhage
- 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% 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.

Note: To expand properly HepaSphere Microspheres need to be exposed to a minimum of 10 ml of solution for doxorubicin HCl or saline and a minimum of 5 ml for irinotecan. 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 and about 30% when loaded with irinotecan.

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 irinotecan, or loaded with doxorubicin HCl solution or irinotecan 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 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.



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

OPTION 1: PREPARATION FOR EMBOLIZATION WITHOUT DRUG (BLAND)

The approximate reconstitution time when used without loading of a drug is 10 min.

- Fill a 10ml syringe with 100% NaCl 0.9% aqueous solution or non-ionic 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 (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, 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 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. 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) or irinotecan (see below Option 3).

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

OPTION 2: PREPARATION FOR EMBOLIZATION 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 lyophilized doxorubicin HCl solubilized 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-solubilized 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 75mg can be loaded into each vial of 25 mg HepaSphere Microspheres. Solubilize the desired dose of lyophilized doxorubicin HCl in 20ml 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 20ml of doxorubicin HCl solution into two separate 30ml syringes. Each 30ml syringe should contain 10ml of doxorubicin HCl solution.
- Connect one of the 30ml syringes containing 10ml 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 30ml syringes containing 10ml 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 minutes 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 minutes hydration period, attach a 20 gauge or larger needle to the second 30ml syringe containing the remaining 10ml 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 20ml of non-ionic contrast medium to the 30ml syringe containing the doxorubicin HCl loaded HepaSphere Microspheres, however larger volume of solution can provide better control during embolization. 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.



OPTION 3: PREPARATION FOR EMBOLIZATION LOADED WITH IRINOTECAN

HepaSphere Microspheres loaded with irinotecan are only applicable to the 30-60µm and 50-100µm sizes.

As a general guideline the loading of irinotecan into HepaSphere Microspheres will take 30 minutes. The HepaSphere Microspheres should not be used before they are fully hydrated and expanded.

- Choose the appropriate dose of irinotecan solution to load into the HepaSphere Microspheres. A maximum dose of 100 mg irinotecan can be loaded in each vial of 25 mg HepaSphere MicroSpheres. Irinotecan solution is typically available in a concentration of 20 mg/ml.
- Aspirate the irinotecan into a syringe connected 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 the syringe containing the irinotecan solution through the stopper of the vial. Continue rolling the vial in your fingertips and inject the irinotecan 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 30 minutes in order to completely hydrate the spheres.
- During those 30 minutes, 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 30 minutes hydration and loading period, attach a 20 gauge or larger needle to an appropriately sized syringe and insert it into the HepaSphere Microspheres vial. Aspirate the contents of the HepaSphere Microspheres vial into the syringe. 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.
- Add an equal volume of non-ionic contrast medium to the syringe containing the irinotecan loaded HepaSphere Microspheres immediately before use.
- Larger volume of non-ionic contrast media can lead to irinotecan release into the supernatant.
- Gently invert the syringe 2 or 3 times and wait 5 min until solution homogeneity is reached.
- Before any injection, check that the microspheres are in suspension. If not, invert the syringe back and forth to disperse contents within the syringe.
- Do not remove the supernatant.



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 doxorubicin/irinotecan/bland loaded 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 the doxorubicin/irinotecan/bland 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/irinotecan/bland loaded 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.

- Invert 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 doxorubicin/irinotecan/bland 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 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 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 labeling.

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.



Size of dry products (µm)	Colour code (label borders)	Quantity of microspheres (mg)	Reference
30-60	Orange	25 50	V 225 HS V 250 HS
50-100	Yellow	25 50	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

INFORMATION ON PACKAGING

Symbol	Designation
	Manufacturer: Name & Address
	Use by date: year-month-day
	LOT Batch code
REF	Catalog number
	Do not re-sterilize
	Do not use if package is damaged
	Keep away from sunlight
	Keep dry
	Do not re-use
	Caution: Consult accompanying documents
	Non-pyrogenic
	Sterilized using irradiation
	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.

LIFEPEARL™ INDICATIONS

The CE Mark approved indication statement for LifePearl™ is for bland embolisation only. The “note”^{*} does not change the CE Mark approved indication statement, which is the statement that includes the words “indicated for” or “intended”.

LifePearl™ Microspheres are indicated for embolization of blood vessels supplying primary-hypervascular tumors or for metastases in the liver.

Note: LifePearl™ can be loaded with chemotherapeutic drugs. 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.

Full LifePearl™ IFU on pages 25 to 27

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* The “note” was added to the IFU *after* CE Mark approval was given by Terumo’s notified body. The declaration of conformity submitted as part of the CE Mark approval process and early copies of the IFU did not contain it (source: correspondence on file at Biocompatibles UK Ltd, a BTG International group company).

Indicated for loading with doxorubicin ❌

Indicated for loading with irinotecan ❌

**INSTRUCTIONS FOR USE**

Carefully read all instructions prior to use.

DESCRIPTION:

LifePearl™ device comprises a range of embolizing microspheres that are biocompatible, hydrophilic, precisely calibrated and capable of loading and releasing chemotherapeutic agents (such as Doxorubicin and Irinotecan) in a controlled manner.

LifePearl™ microspheres are produced from a biocompatible hydrogel comprising of polyethylene glycol and are available in the following size ranges:

Size Range	Label Color
100±25 µm	Black
200 ± 50 µm	Yellow
400 ± 50 µm	Blue

PRESENTATION:

- LifePearl™ microspheres are offered in a 20 ml syringe pre-filled with 2 ml of product suspended in a non-pyrogenic, sterile transport solution of physiological buffered saline.
- Total volume of physiological buffered saline and LifePearl™ microspheres is approximately 6ml.
- Prefilled syringes of LifePearl™ microspheres are packaged in a sterile, sealed tray with a peel-away lid.
- A color coded label indicates the specific size of the microspheres contained in the syringe.

INTENDED USE/INDICATIONS:

LifePearl™ Microspheres are indicated for embolization of blood vessels supplying primary-hypervascular tumors or metastases in the liver.

Note: LifePearl™ can be loaded with chemotherapeutic drugs. 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 - LifePearl™:

1. Targeted embolization of blood vessels belonging to the central vascular system (arteriae pulmonles, aorta ascendens, arcus aorta, aorta descendens to the burticatio aortae, arteriae coronariae, arteria carotis communis, arteria carotis externa, arteria carotis interna, arteriae cerebrales, truncus brachiocephalicus, venae cordis, venae pulmonales, vena cava superior, vena cava inferior).
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 feeding arteries smaller than distal branches from which they emerge.
7. Presence of collateral vessel pathways potentially endangering normal territories during embolisation.
8. Presence of arteries supplying the lesion not large enough to accept LifePearl™ microspheres.
9. Vascular resistance peripheral to the feeding arteries precluding passage of LifePearl™ microspheres into the lesion.
10. Patient is pregnant.
11. Patient has known allergies to radio-opaque contrast agent, drugs and their additives.
12. Do not use LifePearl™ microspheres in the following applications:
 - i. Embolisation of non-malignant tumours.
 - ii. Embolisation 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).
 - iii. Any vasculature where LifePearl™ microspheres could pass directly into non-target territories.

**CAUTIONS:**

- Select the size and quantity of LifePearl™ microspheres appropriate for
- Embolisation with LifePearl™ microspheres should only be performed by a physician with appropriate interventional training.
- Each package of LifePearl™ 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 LifePearl™ 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 LifePearl™ microspheres.
- Proximal slowing and termination of flow may indicate that the vessel or the target area is occluded. Careful fluoroscopic monitoring is required.
- Microparticle 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 LifePearl™ microspheres that have been improperly stored or mishandled.
- If arteriovenous anastomoses, branch vessels which lead away from the targeted embolization area, or emergent not evident prior to embolization are present. it 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 formation 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.

POTENTIAL COMPLICATIONS/WARNINGS

Vascular Embolisation is a high risk procedure. The procedure should be plications can occur at any time during or after the procedure and may include, but not limited to:

- Undesirable reflux or passage of LifePearl™ microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
- Non-target embolization.
- Pulmonary embolization.
- Ischemia at an undesirable location.
- Capillary bed saturation and tissue damage.
- Ischemic stroke or ischemic infarction.
- Vessel or lesion rupture and haemorrhage.
- 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 incision site for arterial access.
- Deep vein thrombosis or clotting of a deep vein in a patient's leg.
- Thrombosis of the artery at the incision site for arterial access.



- 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 LifePearl™ microspheres in conjunction with embolization devices based on organic solvents such as ethyl alcohol and dimethyl sulfoxide (DMSO) at the same embolization site.

INTERACTIONS WITH PHARMACEUTICALS

- There are no known chemical interactions between LifePearl™ microspheres and pharmaceuticals.

DRUG SELECTION AND LOADING:

- LifePearl™ microspheres can load and deliver drugs that may be useful in the treatment of diseases in which embolization is also effective.
- For drug loading please refer to attached instructions for drug loading.

INSTRUCTIONS FOR USE

- Prior to the embolization procedure, evaluate the vascular anatomy associated with the lesion using high resolution imaging.
- LifePearl™ 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.
- LifePearl™ microspheres can tolerate temporary compression of 20-30 % to facilitate passage through a delivery catheter.
- Utilize catheter's minimum inner diameter measurement to determine the catheter compatibility with the microspheres. Carefully evaluate the vascular network associated with the lesion using high resolution imaging prior to beginning the embolisation procedure.
- LifePearl™ microspheres are available in a range of sizes. Care should be taken to choose the appropriate size of LifePearl™ microspheres that best matches the pathology (ie. vascular target vessel size) and provides the desired clinical outcome.

- Choose a delivery catheter based on the size of the target vessel. LifePearl™ microspheres can tolerate temporary compression of 20% to 30% in order to facilitate passage through the delivery catheter.
- 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.
- LifePearl™ microspheres are not radio-opaque. It is recommended to monitor the embolisation under fluoroscopic visualization by adding the desired amount of contrast medium to the suspension fluid.
- Take care to ensure proper suspension of the LifePearl™ microspheres in the contrast medium to enhance distribution during injection.
- Slowly inject LifePearl™ microspheres into the delivery catheter under fluoroscopic visualization while observing the contrast flow rate. Exercise conservative judgment in determining the embolisation endpoint.
- Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge LifePearl™ microspheres still within the catheter lumen.
- Discard any unused LifePearl™ microspheres.

CONSERVATION AND STORAGE:

- Store unopened LifePearl™ microspheres in a cool, dry and dark place in its original packaging.
- Use by the date indicated on the syringe / tray label.
- Do not freeze.

TANDEM™ INDICATIONS

The CE Mark indication statement for Tandem™ is for bland embolisation only.

3.1 Indications

Embozene TANDEM™ Microspheres are indicated for embolization of the following conditions:
Uterine fibroids.

- Hepatocellular carcinoma.
- Tumors of head, neck, torso, and skeletal system.
- Bleeding and trauma.
- Pre-operative reduction of bleeding other than in the central nervous system.

Full Tandem™ IFU on pages 29 to 33

Tandem™ instructions for use LA50048-01. Available at <http://celonova.com/wp-content/uploads/LAS0048-01-Artwork-08-02-20132.pdf> (last accessed 9 May 2016)

Indicated for loading with doxorubicin ❌

Indicated for loading with irinotecan ❌



INSTRUCTIONS FOR USE

1. Product Description

Embozene TANDEM® Microspheres are spherical, tightly calibrated, biocompatible, non-resorbable, hydrogel microspheres coated with an inorganic perfluorinated polymer (Polyzene®-f). They are available in a range of sizes suitable for embolic therapy.

Embozene TANDEM® Microspheres are opaque in color and available in three sizes. Embozene TANDEM® Microspheres may be loaded with drugs (such as doxorubicin hydrochloride or irinotecan hydrochloride) and then can elute a local, controlled, sustained dose of a drug to targeted tumor sites after embolization. They are presented in prefilled syringes, with a choice of 2 ml or 3 ml of product. Embozene TANDEM® Microspheres may be ordered using the product reference numbers listed in Table A.

Table A. Product Specifications and Ordering Information for Embozene TANDEM® Microspheres

Nominal Size	Label Color	Design Specification	Minimum Inner Diameter Required for Catheter	Ref Numbers 2 ml Syringe	Ref Numbers 3 ml Syringe
40µm	Black	40µm ± 10µm	0.002inches	10420-TSO	10430-TSO
75µm	Burgundy	75µm ± 15µm	0.003inches	10720-TSO	10730-TSO
100µm	Orange	100µm ± 25µm	0.004inches	11020-TSO	11030-TSO

2. Presentation

Embozene TANDEM® Microspheres are offered in a 20 ml syringe prefilled with either 2 ml or 3 ml of product suspended in a nonpyrogenic, sterile transport solution of physiological saline. The total volume of Embozene TANDEM® Microspheres, including transport solution, is approximately 7 ml. Prefilled syringes of Embozene TANDEM® Microspheres are packaged in a sterile, sealed tray with a peel-away lid. A color-coded label indicates the specific size of the microspheres contained in the syringe (see Table A).

3. Indications and Contraindications

3.1 Indications

Embozene TANDEM® Microspheres are indicated for embolization of the following conditions:

- Hypervascular tumors.
- Arteriovenous malformations.
- Uterine fibroids.
- Hepatocellular carcinoma.
- Tumors of head, neck, torso, and skeletal system.
- Bleeding and trauma.
- Pre-operative reduction of bleeding other than in the central nervous system.

3.2 Contraindications

Embolization procedures shall not be performed if:

- Patient is unable to tolerate vascular occlusion procedures.
- Vascular anatomy precludes correct catheter placement or embolic injection.
- Presence or likely onset of vasospasm.
- Presence of a blood coagulation disorder that would prohibit arterial punctures.
- Presence of severe atheromatous disease that would preclude correct catheter placement.
- Presence of patent extra-to-intra-cranial anastomoses or shunts from the arterial to the venous circulation.
- Presence of collateral vessel pathways which could potentially endanger non-targeted tissue during an embolization procedure.
- Presence of any vasculature where Embozene TANDEM® Microspheres could pass directly into the central nervous system, central circulatory system or other non-target territories.
- Patient has high-flow arteriovenous shunt with diameter greater than the selected Embozene TANDEM® Microspheres.
- Patient is pregnant.
- Patient has known allergies to barium sulfate, 3-aminopropyltrialkoxysilane, polyphosphazene, IV radiopaque contrast agent, or the drugs and their additives (see corresponding instructions for use).



4. Warnings | Precautions

4.1 Warnings

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

- Undesirable reflux or passage of Embozene TANDEM® Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
- Embolization of the wrong artery or migration of the microspheres to other parts of the body, which may necessitate further treatment.
- Hematoma, or bruising, at the incision site for arterial access.
- Arterial aneurysm at the incision site for arterial access.
- Deep vein thrombosis, or dotting of a deep vein in patient's leg(s).
- Thrombosis of the artery at the incision site for arterial access.
- Pulmonary embolization.
- Ischemia at an undesirable location.
- Capillary bed saturation and tissue damage.
- Ischemic stroke or ischemic infarction.
- Vessel or lesion rupture and hemorrhage.
- Neurological deficits including cranial nerve palsies.
- Vasospasm.
- Recanalization.
- Foreign body reactions necessitating medical intervention.
- Infection necessitating medical intervention.
- Clot formation at the tip of the catheter and subsequent dislodgement.
- Allergic reaction.
- Risks of radiation from angiography and fluoroscopy used to visualize the blood vessels during embolization, which may include a radiation burn and risks to future fertility.
- Death.

- For gynecological embolizations, including fibroid embolization, risks include expulsion of a fibroid tumor or embolization materials from the uterus through the vagina after the procedure, amenorrhea following the procedure, worsening of fibroid-related symptoms or the onset of new symptoms, premature menopause, infection of the endometrium or other structures in the pelvis, which, if severe, could require a hysterectomy, and rupture of the uterus.

Do not use Embozene TANDEM® Microspheres in conjunction with embolization devices based on organic solvents such as ethyl alcohol or dimethyl sulfoxide (DMSO) at the same embolization site.

Do not use ionic contrast agent with this product. Ionic contrast agents could alter the microsphere characteristics resulting in microsphere deformation and procedure failure.

4.2 Precautions

To maintain safety, the following precautions shall be considered:

- Each package of Embozene TANDEM® Microspheres is intended for single patient use only. Discard any unused material. Do not resterilize.
- Physicians using Embozene TANDEM® Microspheres should have appropriate training and experience in a related interventional procedure.
- The physician should carefully select the size and quantity of Embozene TANDEM® Microspheres according to the lesion to be treated based on the physician's seduction and training and currently available scientific evidence.
- Physicians must decide the most appropriate time to stop the infusion of Embozene TANDEM® Microspheres. Typically the artery will accept fewer Embozene TANDEM® Microspheres as the treatment progresses. Proximal slowing or termination of flow may indicate that the vessel or the target area is occluded by Embozene TANDEM® Microspheres. Careful fluoroscopic monitoring is required.
- Microparticle 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 embolization of other non-target healthy tissue or organs.



- Do not use Embozene TANDEM® Microspheres if the sterile barrier, the syringe, or the package appears to be opened or damaged prior to use.
- Do not use Embozene TANDEM® 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, it can lead to non-targeted embolization and cause severe complications for the patient.
- Particles smaller than 100µm 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 formation and more severe post-embolization syndrome.
- Ischemia of tissue adjacent to the targeted 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 the 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.

5. Interaction with Pharmaceuticals

There are no known chemical interactions between Embozene TANDEM® Microspheres and pharmaceuticals.

6. Instructions for Use

6.1 Pre-Procedure Evaluation

Prior to the embolization procedure, evaluate the vascular anatomy associated with the lesion using high resolution imaging.

6.2 Catheter Selection

Embozene TANDEM® Microspheres are designed to be used with a variety of catheters and microcatheters. Select a delivery catheter of appropriate size, suitable for the dimensions of the target vessels. Embozene TANDEM® Microspheres can tolerate temporary compression to facilitate passage through the delivery catheter. Utilize the catheter's minimum inner diameter measurement to determine catheter-to-microsphere compatibility. You may use Table A as a reference.

6.3 Procedure Preparation

1. Carefully select the size of Embozene TANDEM® Microspheres according to the size of the vessel identified and catheter used.
2. Verify that the sterile packaging was not previously compromised.

6.4 Drug Selection and Loading

Embozene TANDEM® Microspheres can load and deliver drugs that may be useful in the treatment of diseases in which embolization is also effective. For drug selection and loading guidelines, see *Embozene TANDEM® Microspheres Loading Guidance*.



6.5 Contrast Mixing and Microsphere Delivery

1. Position the catheter at the desired site and perform angiography to evaluate the blood supply to the lesion.
2. Prior to adding contrast agent to the drug-loaded microspheres, verify that the supernatant has been removed (if not, refer to *Embozene TANDEM® Microspheres Loading Guidance* for proper removal).
3. Use only non-ionic contrast agents. Pure contrast agent or a mixture of contrast agent and water for injection (WFI) may be used. A mixture is especially recommended when less than 50 mg of drug per ml of microspheres has been loaded or when using contrast agent with iodine concentrations higher than 300 mg iodine/ml. Immediately before delivery, add a minimum of 5 ml pure contrast agent or a mixture of contrast agent and WFI per ml of microspheres to the syringe. The remaining syringe volume may be filled up to the total syringe volume (20 ml).
4. Rotate of gently shake the syringe until homogeneous suspension is achieved.
5. Purge all air from the syringe.
6. Attach the 20 ml syringe to one port of the luer-lock 3-way stopcock and a 1 ml injection syringe to another port of the stopcock. Attach a delivery catheter to the remaining port on the stopcock.
7. Draw the Embozene TANDEM® Microspheres mixture slowly and gently into the injection syringe to minimize the potential of introducing air into the system.
8. Under continuous fluoroscopic control, slowly infuse drug-loaded Embozene TANDEM® Microspheres into the blood stream. Always inject under free flow conditions. To optimize injection through the catheter, it is recommended that the syringe remains in a horizontal position during injection. If desired, flush the catheter with saline or WFI during the intervention. Avoid reflux of Embozene TANDEM® Microspheres as this can lead to embolization of other non-target, healthy tissue, or organs and induce immediate ischemia of the tissue or vessel.
9. Continue infusion until the desired devascularization is achieved, or the desired dose is injected.

10. Once the procedural endpoint is reached, wait for 5 minutes to observe whether the microspheres redistribute themselves and re-establish flow to the target. If flow is re-established and stasis is the desired procedural endpoint, inject an additional volume of microspheres.
11. At the end of the infusion, remove the catheter while maintaining gentle aspiration to avoid dislodging any residual Embozene TANDEM® Microspheres still inside the catheter.
12. Discard any opened Embozene TANDEM® Microspheres.

7. Storage Conditions

- Embozene TANDEM® Microspheres should be stored in a dry, dark and cool place.
- Contents of inner peel-package are sterile and non-pyrogenic provided that the peel-package has not been opened or damaged.
- Product must be used prior to expiration date on label.
- Do not freeze.















8. Limited Warranty

Descriptions or specifications in this document are intended to provide physicians with information relating to the Embozene TANDEM® Microspheres' product description, safe handling procedures, and potential risks inherent to embolization procedures, and do not constitute a guarantee. There is no express or implied warranty, including without limitation, any implied warranty of merchantability or fitness for a particular purpose. Under no circumstances shall Celonova BioSciences, Inc. be liable for any direct, incidental, or consequential damages. No person has the authority to bind Celonova BioSciences, Inc. to any representation or warranty except as specifically set forth herein.

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9. Definitions

 Do Not Resterilize	 Manufacturer	 Single Use
 Keep Dry	 Consult Instructions for Use	 Temperature lower limit
 Keep Away from Sunlight	 Expiration Date	REF Catalog Number
 Authorized Representative in The European Union	 Lot Number	
 Do not Use if Package is Damaged	 Sterilized by Steam	



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