DC Bead LUMI™ Radiopaque Embolic Drug-Eluting Bead

INSTRUCTIONS FOR USE
Version 2

STERILE: SINGLE USE ONLY:
(Do not use if package is opened or damaged)

DESCRIPTION:
DC Bead LUMI™ are precisely calibrated, radiopaque, biocompatible, non-resorbable hydrogel beads. The beads are produced from polyvinyl alcohol and contain a covalently bound radiopaque moiety. The beads are capable of loading and eluting doxorubicin or irinotecan.

DC Bead LUMI™ are manufactured to be inherently radiopaque and visible under imaging (Computed Tomography [CT], Cone Beam Computed Tomography [CBCT] and Fluoroscopy). DC Bead LUMI™ are available in two size ranges:

<table>
<thead>
<tr>
<th>Size</th>
<th>Label Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-150µm</td>
<td>Black</td>
</tr>
<tr>
<td>100-300µm</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

Table 1: Product specifications for DC Bead LUMI™.

PRESENTATION:
- 10ml glass vial
- Each vial contains approximately 2ml of product in sterile phosphate buffered saline. The total volume of DC Bead LUMI™ and sterile physiological saline is approximately 8ml.
- The vial is stopper sealed with a color-coded lid.
- Each package contains a 20mm ViaLoc™ Vented Vial Access Device (Yukon Medical LLC, 4021 Stirrup Creek, Durham, NC USA) for removal of DC Bead LUMI™ from the vial.
- DC Bead LUMI™ is intended for single patient use only. Do not re-sterilize. Discard any unused material.

STORAGE:
- Unopened DC Bead LUMI™ should be stored between 2°C to 25°C, in a dry place in its original packaging. Protect the product from light.
- Use by the date indicated on the vial label.
- Do not freeze.
- Storage and handling of doxorubicin or irinotecan should be in accordance with the respective manufacturer’s instructions.

Storage of doxorubicin-loaded DC Bead LUMI™
- Doxorubicin-loaded DC Bead LUMI™ can be stored in pure contrast agent for 7 days in a refrigerator at 2-8°C or for 4 hours at ambient temperature (not exceeding 25°C) assuming that an aseptic loading process has been completed.

Storage of irinotecan-loaded DC Bead LUMI™
- Once mixed with contrast media, DC Bead LUMI™ loaded with irinotecan must be used immediately.

INDICATIONS:
DC Bead LUMI™ can be used as an embolic agent with or without delivery of doxorubicin or irinotecan.

Unloaded DC Bead LUMI™ is intended to be used for the embolization of non-malignant hypervascular tumors and arteriovenous malformations (AVMs).

For the use in malignant indications:
- DC Bead LUMI™ is primarily intended as an embolic agent for the local treatment of malignant hypervascularised tumor(s) in the liver.
- DC Bead LUMI™ is compatible with doxorubicin for the local treatment of tumors in patients with hepatocellular carcinoma (HCC). Doxorubicin can be loaded prior to embolization and then as a secondary action, the beads will elute a local, controlled and sustained dose to the tumor after embolization.
- DC Bead LUMI™ is also intended to embolize the vessels supplying malignant colorectal cancer metastatised to the liver (mCRC).
- DC Bead LUMI™ is compatible with irinotecan which can be loaded prior to embolization and then as a secondary action, the beads will elute a local, controlled and sustained dose to the liver metastases from colorectal cancer after embolization.

WARNINGS:
- It is the doctor’s responsibility to give due consideration to the details in the drug product marketing authorisation in deciding which drug to load DC Bead LUMI™ 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.
- Doxorubicin or irinotecan alone is not authorised in Canada for use in transarterial chemoembolisation.
- Extravasation and Tissue Necrosis: Extravasation of doxorubicin can result in severe local tissue injury and necrosis requiring wide excision and skin grafting. If signs or symptoms of skin extravasation occur with doxorubicin-loaded DC Bead LUMI™, immediately terminate the procedure and apply ice to the affected area. Ice should be applied to the site intermittently for 15 minutes, 4 times a day for 3 days. If appropriate, administer dextranoxane at the site of extravasation as soon as possible and within the first 6 hours after extravasation.

CONTRAINDICATIONS:
DC Bead LUMI™ is contraindicated in the following situations:
- The use of DC Bead LUMI™ loaded with chemotherapeutic agents is contraindicated in paediatric patients.
- The use of DC Bead LUMI™ loaded with chemotherapeutic agents is contraindicated in patients with Child-Pugh Class C cirrhosis or a serum creatine > 0.18 mmol/L.
- The use of DC Bead LUMI™ loaded with chemotherapeutic agents is contraindicated in patients with renal dysfunction as evidenced by a serum creatine > 0.18 mmol/L.
- Patients intolerant to vascular occlusion procedures.
- Vascular anatomy that precludes catheter placement or injection of embolics.
- Presence or likely onset of vasospasm.
- Presence or likely onset of haemorrhage.
- Presence of severe atheromatous disease.
- Presence of feeding arteries smaller than any distal branch from which they emerge.
- Presence of patent extra-to-intracranial anastomoses or shunts.
- Presence of collateral vessel pathways potentially endangering normal territories during the embolization.
- Presence of end arteries leading directly to cranial nerves.
- Presence of arteries supplying the lesion not large enough to accept DC Bead LUMI™.
- Embolization of non-malignant tumors when loaded with chemotherapeutic drug.
- Presence of high-flow arteriovenous shunt with a diameter greater than the selected bead size that cannot be coiled or blocked.
- Embolization of AV 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 Bead LUMI™ could pass directly into the internal carotid artery or other non-target territories.
- The use of Visipaque (Iodixanol) with irinotecan-loaded DC Bead LUMI™.
- Any neurovascular or central cardiovascular indication.
- Vascular resistance peripheral to the feeding arteries precluding passage of DC Bead LUMI™ into the lesion/tumor.
- Prior biliary surgery, bile duct dilatation or biliary sphincterotomy.
- Do not use in the pulmonary arterial vasculature.

Contraindications when using doxorubicin or irinotecan:
Refer to irinotecan or doxorubicin packaging insert (SmPC) for contraindications regarding use.
Cautions associated with doxorubicin-loaded DC Bead LUMI™

- A recommended dose of 37.5mg doxorubicin per 1ml of DC Bead LUMI™ should not be exceeded. Exceeding the maximum recommended dose may lead to some systemic distribution of doxorubicin and related side effects Up to 4ml doxorubicin loaded DC Bead LUMI™ (total 150 mg) may be used per treatment session. (Lencioni R et al, 2012).
- Evidence from the literature for the equivalent product, DC Bead™, indicates that patients receive between 1 and 5 treatments with DC Bead™ loaded with doxorubicin (up to 150mg/treatment), depending on their clinical and radiologic response. The duration of time between procedures should be between 1 and 2 months with possibly shorter intervals for bilobar disease (see below under “treatment / retreatment”).
- Liposomal formulations of doxorubicin are not suitable for loading into DC Bead LUMI™
- DC Bead LUMI™ beads do not change in size after drug loading.

Cautions associated with irinotecan-loaded DC Bead LUMI™

- A recommended dose of 50mg irinotecan per 1ml of DC Bead LUMI™ should not be exceeded. Exceeding the maximum recommended dose may lead to some systemic distribution of irinotecan and related side effects. Up to 2ml irinotecan-loaded DC Bead LUMI™ (total 100mg) may be used per treatment session (Lencioni R et al, 2014).
- Evidence from the literature for the equivalent product, DC Bead™, indicates that most patients with liver metastases from colorectal cancer receive up to 2 treatments with the equivalent product, DC Bead™, loaded with irinotecan (up to 100mg per treatment), depending on their clinical and radiologic response. The duration of time between procedures should be between 3 - 4 weeks with possibly shorter intervals for bilobar disease (see below under “treatment / retreatment”).
- Several protocols can be used to achieve pain control, including intravenous administration of analgesic agents and intraarterial injection of lidocaine. For the equivalent product, DC Bead™, injection of intraarterial 1% lidocaine (4–10ml split before and near the end of embolization procedure) has been shown to reduce adverse events and hospital length of stay (Martin et al, 2010). The use of bilateral paravertebral block has also been proposed as an effective means for pain control (Marques et al, 2013). Periprocedural medication should be administered at the physician’s discretion according to standard hospital protocols.
- DC Bead LUMI™ beads do not change in size after drug loading.
- It is not recommended that saline solution be added to the irinotecan-loaded DC Bead LUMI™ as this will release irinotecan into the delivery solution potentially leading to systemic delivery of drug.
- DC Bead LUMI™ mixed with contrast agent should be administered immediately after preparation.
- Patients with metastases from colorectal cancer treated with irinotecan-loaded DC Bead LUMI™ may experience more immediate side effects for example, fever, abdominal pain and vomiting, compared with patients who had received an irinotecan-based systemic regimen. Patients treated with systemic chemotherapy however, have a much higher incidence of systemic drug effects such as diarrhoea, ascites, neutropenia, leukopenia and anaemia (Fiorentini et al, 2012).

POTENTIAL COMPLICATIONS:

Undesirable reflux or passage of DC Bead LUMI™ into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
- Non-target embolization, for example:
  - Gastrointestinal ulcerations
  - Pulmonary embolization
  - Pancreatitis, cholecystitis
  - Liver insufficiency, dysfunction or decompensation (a known complication of chemoembolization, but may also result from progression of underlying disease)
  - Deep vein thrombosis, or clotting of a deep vein in patient’s leg(s)
  - Liver vein thrombosis
  - Thrombosis of the artery at the incision site for arterial access
  - 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.
  - 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.
  - Post-embolization syndrome (which may include nausea, fever, pain) and increases in laboratory parameters such as elevated liver enzymes.
  - Liver abscess.
  - Death.
  - Allergic reactions when used in conjunction with contrast agents in patients who are allergic or intolerant to those contrast agents.
  - Embolization of the wrong artery or migration of the microspheres to other parts of the body, which may necessitate further treatment.
  - Haematoma, or bruising, or arterial aneurysm at the arterial access incision site.

DRUG-SPECIFIC UNDESIRABLE EFFECTS

DC Bead™ and DC Bead LUMI™ have been developed in order to offer localised drug delivery to liver tumors with corresponding reduced systemic toxicity. Favourable pharmacokinetic profiles and patient tolerability benefits have been demonstrated in studies with both doxorubicin- and irinotecan-loaded DC Bead™ (Varela et al. 2007, Eichler et al. 2012, Lammer et al. 2010 and Fiorentini et al. 2012). Very few serious drug-related adverse reactions have been reported in relation to the equivalent product (doxorubicin-loaded DC Bead™ or irinotecan-loaded DC Bead™) and non-serious reports tend to be rare and align in type with those seen in the SmPCs for systemic administration of doxorubicin and irinotecan. Please refer to the SmPCs for the corresponding drug for information regarding undesirable effects of the the used drugs doxorubicin or irinotecan.

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CHOICE OF BEAD SIZE:
Care should be taken to choose the appropriate size range of DC Bead LUMI™ that best matches the pathology (i.e. vascular target/vessel size / AVM nidus). Either 100 –300µm or 70-150µm DC Bead LUMI™ are recommended for standard HCC procedures or for the treatment of liver metastases from colorectal cancer. The choice of smaller bead size is based on the demonstration in the equivalent product DC Bead™, that such particles are delivered inside the tumor or in close proximity to the tumor margin and thus are suitable for drug delivery or precise embolization. However, individual patient and tumor characteristics, particularly the identification of arteriovenous shunting, should be taken into account when the safety of the treatment and the choice of DC Bead LUMI™ size are determined. In the case of significant arterioporal or hepatic venous shunting, embolization of the shunt with gelfoam pledges is recommended before proceeding with administration of DC Bead LUMI™. Angiographic confirmation that the shunt is no longer present must be obtained before DC Bead LUMI™ injection can be performed, and a larger bead size using an equivalent bead product may be preferred.

TREATMENT AND RETREATMENT:

HCC treatment with doxorubicin-loaded DC Bead LUMI™:
In patients with residual viable tumor—including partial response, stable disease, and progressive disease according to mRECIST—further treatment with DC Bead LUMI™ (max. of 5 treatments, up to 150mg doxorubicin / treatment) can be scheduled after 4–8 weeks in the absence of contraindications. Obtaining confirmation that the liver enzymes have returned to baseline before repeating treatment is recommended. In bilobar tumors, the two hepatic lobes can be treated in separate treatment sessions 2–4 weeks apart, in the absence of complications requiring a longer time interval between the two sessions. Obtaining confirmation that the liver enzymes have returned to baseline before performing the second treatment session is recommended.

mCRC treatment with irinotecan-loaded DC Bead LUMI™:
In the case of unilobar disease, up to two lobar treatments can be scheduled, each with up to 100mg irinotecan per treatment, separated by 3–4 weeks in the absence of contraindications. Obtaining confirmation that the liver enzymes have returned to baseline levels before performing the second treatment is recommended. For bilobar disease, four lobar treatments should be planned, each with up to 100mg irinotecan-loaded in one DC Bead LUMI™ vial, every 2 weeks in the absence of complications requiring a longer time interval between the two sessions. Obtaining confirmation that the liver enzymes have returned to baseline levels before performing each subsequent treatment is recommended.

LOADING AND ADMINISTRATION OF DC BEAD LUMI™

- Once opened, DC Bead LUMI™ should be used within 4 hours if they are kept at room temperature or within 24 hours if they are stored in a refrigerator at 2-8°C, as the preparation and loading conditions of DC Bead LUMI™ are performed outside of the manufacturer’s control, i.e. storage once the vial has been pierced is under the responsibility of the user.
- Carefully evaluate the vascular network associated with the site to be embolized using high-resolution imaging prior to beginning the embolization procedure. Care should be taken to choose the appropriate size range of DC Bead LUMI™ that best matches the pathology (i.e. vascular target/vessel size / AVM nidus)
- When removing the vial from outer packaging, visually inspect for breakage or sharp edges prior to use.
- Use appropriate protective clothing and hygiene measures.
- Choose a delivery catheter based on the size of the target vessel. Use the catheter’s minimum inner diameter measurement to determine catheter-to-microsphere compatibility. Minimum catheter sizes are given in table 6.
- It is recommended to monitor the embolization procedure using X-ray imaging techniques such as CT, CBCT and fluoroscopy.

Notes:
- It is recommended to use non-ionic contrast agent during the delivery of DC Bead LUMI™. Throughout the preparation, avoid the introduction of air bubbles. If air bubbles are observed, eliminate them to prevent potential aggregation of the microspheres.
- DC Bead LUMI™ are suitable for loading with doxorubicin or irinotecan.

CAUTION: Due to the cytotoxicity of the chemotherapeutic agents

Preparation of DC Bead LUMI™:
1. During preparation of DC Bead LUMI™, use controlled aseptic conditions.
2. Remove the plastic color-coded flip cap from DC Bead LUMI™ vial but do not remove the metal ring around the stopper. With the spike of the ViaLok™ Vented Access Device centred to the rubber stopper of the vial, attach the device until the retention tabs snap on the DC Bead LUMI™ vial.
   Note: The ViaLok™ Vented Access Device is not for direct infusion and should only be used for transfer of the beads into a syringe. The access device size corresponds to vial diameter and is intended for use with ISO-594 compatible mating Luers. DC Bead LUMI™ has only been tested in conjunction with ViaLok™ Vented Access Device.
3. Remove and discard luer cap from the access device.
   Note: To minimise risk of potential contamination, the ViaLok™ Vented Access Device protective cap shall remain attached to Luer until accessed by the mating Luer device.
4. Attach a 10ml syringe to the luer lock of the ViaLok™ Vented Access Device.
5. Invert vial and suspend the beads in solution by agitating in a swirling motion whilst drawing the DC Bead LUMI™ into the syringe.
6. Once all the solution is transferred, discontinue the agitation and maintain the vial in the inverted position to allow the beads to settle in the syringe on the plunger. Return only the clear solution to the vial and repeat previous step to recover remaining beads from the vial. This process may be repeated twice if required.
   Note: Small traces of DC Bead LUMI™ may be retained in the vial.
7. Once DC Bead LUMI™ has settled at the bottom of the syringe, disconnect the syringe from the ViaLok™ Vented Access Device. Expel all packing solution to waste or suitable container, leaving only DC Bead LUMI™ within the syringe.

Drug loading procedure (if no drug loading is performed, proceed with point 12. under “Mixing with contrast agent”):
8. Handle the drug according to manufacturer’s guidelines. For reconstitution of doxorubicin powder, use water for injection (WFI) to achieve a concentration of 25mg/ml. Please use doxorubicin powder for loading, as doxorubicin solutions have not been tested with DC Bead LUMI™. For irinotecan loading please use irinotecan solution (20 mg/ml).
9. Transfer the required amount of reconstituted drug into the syringe containing DC Bead LUMI™ and agitate. Take care that the syringe is properly sealed so as not to spill cytotoxic drug. Make sure beads are mobile when inverting beads during loading. Do not exceed the recommended maximum loading dose:
   - 37.5mg of doxorubicin per 1ml of DC Bead LUMI™ (equivalent to 75mg per vial).
   - 50mg of irinotecan per 1ml of DC Bead LUMI™ (equivalent to 100mg per vial).
10. Follow the loading instructions as given in tables 4 and 5.

Table 4: Drug loading instructions doxorubicin

<table>
<thead>
<tr>
<th>Bead size</th>
<th>Loading time (min)</th>
<th>No of syringe inversion per agitation step</th>
<th>Agitation interval during loading (min)</th>
<th>Loading temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-150 µm</td>
<td>60 minutes</td>
<td>10</td>
<td>5</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>100 –300µm</td>
<td>90 minutes</td>
<td>10</td>
<td>5</td>
<td>Room Temperature</td>
</tr>
</tbody>
</table>

Table 4: Drug loading instructions doxorubicin
11. After doxorubicin loading the solution may retain some coloration which is to be expected and is not an indication that DC Bead LUMI™ has failed to load.

12. Expel the excess liquid into a suitable container for cytotoxic waste, following the local standard practice and the cytotoxic drug manufacturer’s guidance retaining a total volume of 2ml of loaded beads. For this hold the syringe in an inverted position to let the beads settle on the plunger. Ensure that beads are settled prior to expelling the supernatant. Caution is required when expelling the depleted cytotoxic solution into an appropriate container such as an empty safety-vented bunged vial, a septum solution bag, a second syringe via a two-way luer connector etc.

**WARNING (Doxorubicin loading):** Strict adherence to the instructions, loading times and process will ensure >98% drug loading. The product should not be used in the event of an intensely red opaque supernatant as this is an indication of inadequate loading or excess of added doxorubicin.

**Mixing with contrast agent:**

13. DC Bead LUMI™ is now ready for use.

14. DC Bead LUMI™ should be prepared for administration using 100% non-ionic contrast agent to obtain an optimum suspension. Please refer to table 6 for recommended contrast agents.

15. Attach a connector to the syringe containing DC Bead LUMI™. Using a 20ml syringe take up 20ml of contrast agent and connect to the 10ml syringe containing the DC Bead LUMI™.

16. Gently mix DC Bead LUMI™ and contrast agent between syringes through the connector, until a homogenous suspension is achieved.

17. Remove 20ml syringe and replace with 3ml syringe for delivery. Mix between the 10ml and 3ml syringes using a connector to obtain homogeneous suspension of DC Bead LUMI™. After the contents of the 10ml syringe is delivered, the process can be repeated by transferring the remaining suspension from the 20ml syringe to the 10ml syringe through a connector.

Note: Please ensure mixing is performed between each refill of the 3ml syringe.

**Recommended Catheters and Contrast Agents:**

Once prepared, DC Bead LUMI™ has been tested and shown to be successfully delivered using the combinations of bead size, contrast medium and microcatheters shown in Table 6.

### Table 5: Drug loading instructions irinotecan

<table>
<thead>
<tr>
<th>Bead size</th>
<th>Loading temperature (°C)</th>
<th>Agitation interval during loading (min)</th>
<th>Loading time (min)</th>
<th>No of syringe inversion per agitation step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan Hydrochloride</td>
<td>Room Temperature</td>
<td>5 minutes</td>
<td>10 minutes</td>
<td>10</td>
</tr>
<tr>
<td>70-150 µm (70–170µm)**</td>
<td>Room Temperature</td>
<td>5 minutes</td>
<td>10 minutes</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 6: Recommended catheter sizes and contrasts agents for application with DC Bead LUMI™.

**Delivery Instructions:**

**Note:**

Please note that DC Bead LUMI™ will settle quickly in some contrast agents. Prior to and during delivery, ensure visually that the beads are in suspension. Please note that larger beads have shorter suspension times than the smaller size range of DC Bead LUMI™.

1. Using standard techniques, position the delivery catheter within the target vessel and the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of non-target vessels.

2. Use a 3ml syringe to manage the injection pressure during catheter delivery of the DC Bead LUMI™ microspheres.

3. Slowly inject DC Bead LUMI™ solution into the delivery catheter under X-ray techniques such as fluoroscopy, CBCT and CT imaging while observing the bead distribution to avoid reflux. If there is no effect on the antegrade flow rate, choose a larger size of DC Bead LUMI™ (if applicable) and repeat the delivery process. Exercise conservative judgment in determining the embolization endpoint.

4. Where necessary, saline flushes can be used to ensure full delivery of the DC Bead LUMI™.

5. Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge DC Bead LUMI™ that may still be within the catheter lumen.

6. Discard any open unused DC Bead LUMI™ as well as any other ancillary equipment used in the procedure such as the ViaLok™ Vented Access Device, syringes, needles, catheters, etc. according to applicable local standard practice and the cytotoxic drug manufacturers guidelines to dispose of cytotoxics and clinical waste.

**PACKAGE LABEL:**

- Catalogue number
- Batch number/Lot number
- Do not reuse
- Steam Sterilized
- Use-by date/Expiry
- Protect from light/keep away from sunlight
- Protect from moisture/keep dry
- Do not freeze. Store at 2-25°C.
REFERENCES:


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