DC Bead™/DC BeadM1™ Embolic Drug-Eluting Bead

INSTRUCTIONS FOR USE
Version 9

STERILE:SINGLE USE ONLY:NON-PYROGENIC

DESCRIPTION:
DC Bead™ and DC BeadM1™ comprise a range of hydrogel beads that are biocompatible, hydrophilic, non resorbable, size calibrated and capable of loading and eluting doxorubicin or irinotecan. DC Bead™ and DC BeadM1™ are produced from polyvinyl alcohol and are available in the following size ranges:

<table>
<thead>
<tr>
<th>Product</th>
<th>Nominal Bead Size</th>
<th>Colour Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC BeadM1™</td>
<td>100-500µm</td>
<td>Black</td>
</tr>
<tr>
<td>DC Bead™</td>
<td>70-150µm</td>
<td>Yellow</td>
</tr>
<tr>
<td></td>
<td>300-500µm</td>
<td>Blue</td>
</tr>
<tr>
<td></td>
<td>500-700µm</td>
<td>Red</td>
</tr>
</tbody>
</table>

Table 1: Available size ranges of DC Bead™/DC BeadM1™

PRESENTATION:
- 10ml glass vial.
- Each vial contains approximately 2ml of DC Bead™/DC BeadM1™ in 6ml non- pyrogenic, sterile, physiological buffered saline.
- The vial is stopper sealed by an aluminium cap with a colour-coded lid.
- Each vial is intended for single patient use only. Do not resterilise.
- Discard any unused material.

STORAGE:
- Store unopened DC Bead™ and/or 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.
- Storage and handling of doxorubicin or irinotecan should be in accordance with the respective manufacturer’s instructions.

INDICATIONS:
DC Bead™ and DC BeadM1™ are primarily intended as an embolic agent for the local treatment of malignant hypervascularised tumour(s) in the liver.

DC Bead™ and DC BeadM1™ are compatible with doxorubicin for the local treatment of tumours in patients with hepatocellular carcinoma (HCC). Doxorubicin can be loaded prior to embolisation and as a secondary action, will elute a local, controlled and sustained dose to the tumour after embolisation.

DC Bead™ and DC BeadM1™ are also intended to embolise the vessels supplying malignant colorectal cancer metastasised to the liver (mCRC).

DC Bead™ and DC BeadM1™ are compatible with irinotecan which can be loaded prior to embolisation and as a secondary action, elute a local, controlled and sustained dose to the liver metastases from colorectal cancer after embolisation.

WARNINGS:
- The use of doxorubicin or irinotecan-loaded DC Bead™/DC BeadM1™ represents an unlicensed method of administration of these medicinal products.
- It is the doctor’s responsibility to give due consideration to the details in the drug product marketing authorisation in deciding which drug (either doxorubicin or irinotecan) to load DC Bead™/DC BeadM1™ 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.
- 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™/DC BeadM1™, immediately terminate the procedure. If appropriate, administer dexrazoxane at the site of extravasation as soon as possible and within the first 6 hours after extravasation.
- Systemic exposure to doxorubicin or irinotecan can occur. Related side effects that might occur are listed below in section “Undesirable effects related to use of chemotherapy drugs”.
- Due to the known cytotoxic, mutagenic and embryotoxic properties of doxorubicin and embryotoxic / teratogenic properties of irinotecan, drug-loaded DC Bead™/DC BeadM1™ should not be used during pregnancy unless clearly necessary, women should not breastfeed and women / men of childbearing potential should use adequate contraceptive measures as outlined in the relevant Summary of Product Characteristics (SmPC).

CONTRAINDICATIONS:
DC Bead™/DC BeadM1™ is contraindicated in the following situations:
- The use of DC Bead™/DC BeadM1™ loaded with chemotherapy agents is contraindicated in paediatric patients.
- The use of DC Bead™/DC BeadM1™ loaded with chemotherapy agents is contraindicated in patients with Child-Pugh Class B (≥ 8) and Class C cirrhosis or a bilirubin level ≥ 3.0 mg/dl
- The use of DC Bead™/DC BeadM1™ loaded with chemotherapy agents is contraindicated in patients with renal dysfunction as evidenced by a serum creatinine >2.0 mg/dl.
- 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 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™/DC BeadM1™.
- Embolisation of non-malignant tumours 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.
- Embolisation in the presence of large diameter arteriovenous (AV) shunts.
- Embolisation of AV shunts (ie where the blood does not pass through the arterial/capillary/venous transition but directly from artery to vein).
- Any vasculature where DC Bead™/DC BeadM1™ embolic agent could pass directly into the internal carotid artery or other non-target territories.
- Vascular resistance peripheral to the feeding arteries precluding passage of DC Bead™/DC BeadM1™ into the tumour.
- Prior biliary surgery, bile duct dilatation or biliary sphincterotomy.
- The use of Visipaque (Iodixanol) with irinotecan-loaded DC Bead™/DC BeadM1™.

Contraindications: Use of doxorubicin and irinotecan:
See irinotecan or doxorubicin package insert for contraindications regarding use.

CAUTIONS:
- Do not use if the vial or packaging appear damaged.
- Select the size and quantity of DC Bead™/DC BeadM1™ appropriate for the pathology to be treated. Regarding actual bead sizes for administration please refer to table 6 (section “Delivery instructions”). Please note that a small number (< 5%) of beads may be outside the indicated ranges. The physician should be sure to carefully select the size of the beads according to the size of the target vessels and the desired clinical outcome.
Cautions associated with DC Bead™/DC Bead™ M1

- Ensure that DC Bead™/DC Bead™ M1 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 Te99m-MAA scanning if there is suspicion of AV shunting.
- Monitor patients carefully for signs of non-target embolisation such as hypoxia or central nervous system changes.

Cautions associated with doxorubicin-loaded DC Bead™/DC Bead™ M1

- A recommended dose of 37.5mg doxorubicin per 1ml of DC Bead™/DC Bead™ M1 should not be exceeded. Exceeding the maximum recommended dose may lead to significant systemic exposure to doxorubicin and related side effects. Up to 4ml doxorubicin-loaded DC Bead™/DC Bead™ M1 (total 150mg) may be used per treatment session (Lencioni et al, 2012).
- Systemic exposure to doxorubicin can also occur with this standard dosage of DC Bead™/DC Bead™ M1. However, pharmacokinetic data have shown that systemic exposure levels are significantly reduced compared to conventional transarterial chemoembolization and intravenous administration (AUC of approximately 520 hours.ng/ml for DC Bead™ vs 10,200 hours.ng/ml for intravenous doxorubicin). Pharmacokinetic data have also shown that systemic exposure to irinotecan can occur with this standard dosage of DC Bead™/DC Bead™ M1. However, pharmacokinetic data have shown that systemic exposure levels are significantly reduced compared to conventional transarterial chemoembolization and intravenous administration (AUC of approximately 600 hours.ng/ml for DC Bead™ vs 72,000 hours.ng/ml for intravenous irinotecan).

- Evidence from the literature indicates that patients receive between 1 and 5 treatments with DC Bead™/DC Bead™ M1 loaded with doxorubicin (up to 150mg/treatment), depending on their clinical and radiologic response. The time between procedures should be between 1 and 2 months with possibly shorter intervals for bilateral disease (see below under “treatment/retreatment”).
- The size diameter of doxorubicin-loaded DC Bead™/DC Bead™ M1 will reduce after loading. The actual bead sizes for administration are shown in table 6 for the different size ranges and drugs that may be loaded (section “Delivery instructions”). A corresponding volume reduction will also occur.
- Doxorubicin-loaded DC Bead™/DC Bead™ M1 should be used immediately when using Isovep (Iopamidol).
- Doxorubicin is sensitive to light. Storage of doxorubicin loaded product should be protected from light (see “loading instructions”).

Cautions associated with irinotecan-loaded DC Bead™/DC Bead™ M1

- A recommended dose of 50mg irinotecan per 1ml of DC Bead™/DC Bead™ M1 should not be exceeded. Exceeding the maximum recommended dose may lead to significant systemic exposure to irinotecan and related side effects. Up to 2ml irinotecan-loaded DC Bead™/DC Bead™ M1 (total 100mg) may be used per treatment session (Lencioni et al, 2014). Systemic exposure to irinotecan can also occur with this standard dosage of DC Bead™/DC Bead™ M1. However, pharmacokinetic data have shown that systemic exposure levels are significantly reduced compared to intravenous administration (AUC of approximately 1680 hours.ng/ml for DC Bead™ vs 10,200 hours.ng/ml for intravenous irinotecan). Systemic exposure to SN-38 (AUC approximately 280 hours.ng/ml), is within the expected AUC range for IV irinotecan treatment of colorectal cancer.

- Evidence from the literature indicates that most patients with liver metastases from colorectal cancer receive up to 2 treatments with DC Bead™/DC Bead™ M1 loaded with irinotecan (up to 100mg per treatment), depending on their clinical and radiologic response. The time between procedures should be between 3 - 4 weeks with possibly shorter intervals for bilobar disease (see below under “treatment/retreatment”).

- The size diameters of the irinotecan-loaded DC Bead™/DC Bead™ M1 will reduce after loading. The actual bead sizes for administration are shown in table 6 for the different size ranges and drugs that may be loaded (section “Delivery instructions”). A corresponding volume reduction will also occur.

- It is not recommended that saline solution is added to the irinotecan-loaded DC Bead™/DC Bead™ M1 as this will release irinotecan into the delivery solution potentially leading to systemic delivery of drug on administration.

- 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.

- Evidence from the literature indicates that patients receive between 1 and 5 treatments with DC Bead™/DC Bead™ M1 loaded with doxorubicin (up to 150mg/treatment), depending on their clinical and radiologic response. The time between procedures should be between 1 and 2 months with possibly shorter intervals for bilateral disease (see below under “treatment/retreatment”).
- Doxorubicin-loaded DC Bead™/DC Bead™ M1 should be used immediately when using Isovep (Iopamidol).
- Doxorubicin is sensitive to light. Storage of doxorubicin loaded product should be protected from light (see “loading instructions”).

Cautions associated with irinotecan-loaded DC Bead™/DC Bead™ M1

- A recommended dose of 50mg irinotecan per 1ml of DC Bead™/DC Bead™ M1 should not be exceeded. Exceeding the maximum recommended dose may lead to significant systemic exposure to irinotecan and related side effects. Up to 2ml irinotecan-loaded DC Bead™/DC Bead™ M1 (total 100mg) may be used per treatment session (Lencioni et al, 2014). Systemic exposure to irinotecan can also occur with this standard dosage of DC Bead™/DC Bead™ M1. However, pharmacokinetic data have shown that systemic exposure levels are significantly reduced compared to intravenous administration (AUC of approximately 1680 hours.ng/ml for DC Bead™ vs 10,200 hours.ng/ml for intravenous irinotecan). Systemic exposure to SN-38 (AUC approximately 280 hours.ng/ml), is within the expected AUC range for IV irinotecan treatment of colorectal cancer.

- Evidence from the literature indicates that most patients with liver metastases from colorectal cancer receive up to 2 treatments with DC Bead™/DC Bead™ M1 loaded with irinotecan (up to 100mg per treatment), depending on their clinical and radiologic response. The time between procedures should be between 3 - 4 weeks with possibly shorter intervals for bilobar disease (see below under “treatment/retreatment”).

- The size diameters of the irinotecan-loaded DC Bead™/DC Bead™ M1 will reduce after loading. The actual bead sizes for administration are shown in table 6 for the different size ranges and drugs that may be loaded (section “Delivery instructions”). A corresponding volume reduction will also occur.

- It is not recommended that saline solution is added to the irinotecan-loaded DC Bead™/DC Bead™ M1 as this will release irinotecan into the delivery solution potentially leading to systemic delivery of drug on administration.

- 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.

- Evidence from the literature indicates that patients receive between 1 and 5 treatments with DC Bead™/DC Bead™ M1 loaded with doxorubicin (up to 150mg/treatment), depending on their clinical and radiologic response. The time between procedures should be between 1 and 2 months with possibly shorter intervals for bilateral disease (see below under “treatment/retreatment”).
- Doxorubicin-loaded DC Bead™/DC Bead™ M1 should be used immediately when using Isovep (Iopamidol).
- Doxorubicin is sensitive to light. Storage of doxorubicin loaded product should be protected from light (see “loading instructions”).
DC Bead™ is allowed in HCC patients with Child-Pugh A or B (< 8) cirrhosis.

Patients with Renal Impairment

Serum creatinine >2.0 mg/dl constitutes an absolute contraindication for TACE procedures (Liap & Geschwind 2011). Patients were excluded from the company sponsored studies if they had renal insufficiency/failure or serum creatinine was higher than 2 mg/dl.

Patients in whom only limited or no data are available on DC Bead™/DC Bead™ with doxorubicin

In the following patient groups, there are limited or no data available on DC Bead™/DC Bead™ with doxorubicin:
- Patients who have received previous systemic chemotherapy
- Patients who have received previous radiotherapy
- Patients with advanced liver disease
- Patients with advanced tumoural disease, including diffuse HCC

Irinotecan-loaded DC Bead™/DC Bead™

Elderly Patients

In clinical practice, no upper age limit is established for use of chemoembolisation procedures whenever patient characteristics and baseline laboratory tests are within those established for such procedures. Recent publications on the use of irinotecan-loaded DC Bead™ in patients with liver metastases from colorectal cancer included patients with mean age of around 64 years of age (range 44-85 years) (Eichler et al 2012, Fiorentini et al 2012). Based on the above information, the use of chemotherapy-loaded DC Bead™/DC Bead™ is allowed in elderly patients.

Patients with Renal Impairment

Serum creatinine >2.0 mg/dl constitutes an absolute contraindication for TACE procedures (Liap & Geschwind, CVIR 2010). Patients were excluded from the company-sponsored studies if they had renal insufficiency/failure or serum creatinine was higher than 2mg/dl.

POTENTIAL COMPLICATIONS:

The frequency of the following complications is comparable to the expected rate for embolisation procedures:

- Very common (≥10%)
  - Post embolisation syndrome (which may include nausea, fever, pain and increases in laboratory parameters such as elevated liver enzymes).

- Common (≥1% to <10%)
  - Liver insufficiency, dysfunction or decompensation (is a known complication of chemoembolisation, but may also result from progression of underlying disease).

- Uncommon (≥0.1% to <1%)
  - Undesirable reflux or passage of DC Bead™/DC Bead™ into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds.
  - Non-target embolisation, for example: - Gastroduodenal ulcerations - Pancreatitis, choledochitis - Vessel or lesion rupture and haemorrhage.
  - Infection necessitating medical intervention.
  - Thrombosis of the artery at the incision site for arterial access
  - Embolisation of the wrong artery or migration of the microspheres to other parts of the body, which may necessitate further treatment.
  - Liver abscess
    - Haematoma or bruising, or arterial aneurysm at the arterial access incision site

- Other potential complications rarely (≥0.01% to <0.1%) or not reported with but are known to occur during embolisation procedures include
  - Pulmonary embolisation as a specific non-target embolisation
  - Ischaemia at an undesirable location.
  - Capillary bed saturation and tissue damage.
  - Ischaemic stroke or ischaemic infarction.
  - Neurological deficits including cranial nerve palsies.
  - Vasospasm.

- Recanalisation.
- Clot formation at the tip of the catheter and subsequent dislodgement causing arterial thromboembolic sequelae.
- Deep vein thrombosis, or clotting of a deep vein in patient’s leg(s)
- Liver vein thrombosis
- Foreign body reactions necessitating medical intervention.
- Allergic reactions when used in conjunction with contrast agents in patients who are allergic or intolerant to those contrast agents.

Death: In a review of the literature < 2% of patients had treatment-related or possibly treatment-related fatal events within 30 days of treatment. This rate is within the threshold (4%) suggested in the quality improvement guidelines for transhepatic arterial chemoembolisation, embolisation and chemotherapeutic infusion for hepatic malignancy (Brown et al, 2012). It should be considered that many patients are seriously ill with advanced cancer and/or cirrhosis, and that their underlying disease may be a substantial factor contributing to their death.

UNDESIRABLE EFFECTS RELATED TO USE OF CHEMOTHERAPY DRUGS WITH DC Bead™/DC Bead™

DC Bead™/DC Bead™ has been developed in order to offer localised drug delivery to liver tumours with corresponding reduced systemic toxicity. 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). Table 2 shows the undesirable effects listed within the product labelling for doxorubicin.

### Table 2: Undesirable Effects Related to Use of Chemotherapy Drugs with DC Bead™/DC Bead™

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms Benign and Malignant (including cysts and polyps)</td>
<td>The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1-3 year) latency period. Acute lymphocytic leukaemia and acute myelogenous leukaemia.</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Haematological monitoring should be undertaken regularly in both haematological and non haematological conditions, because of the possibility of bone-marrow depression which may become evident around ten days from the time of administration. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septicemia, septic shock, haemorrhages, tissue hypoxia or death. Leucopenia, neutropenia, anaemia and thrombocytopenia.</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Anorexia, dehydration and hyperuricaemia.</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Conjunctivitis / keratitis and lacrimation.</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. Routine ECG monitoring is recommended and caution should be exercised in patients with impaired cardiac function. Severe cardiac failure may occur suddenly without premonitory ECG changes. Tachyarrhythmias, atrio-ventricular and bundle branch block, asymptomatic reduction in left ventricular ejection fraction and congestive heart failure.</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Phlebitis, thrombophlebitis, thromboembolism, hot flushes and shock.</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea, vomiting and mucositis/stomatitis, hyperpigmentation of oral mucosa, oesophagitis, abdominal pain, gastric erosions, gastrointestinal tract bleeding, diarrhoea and colitis.</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Changes in transaminase levels.</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally resumes after treatment is</td>
</tr>
</tbody>
</table>
### Table 2: Undesirable Effects listed within the product labelling for doxorubicin

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Delayed diarrhea</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea (occurring more than 24 hours after administration) is a dose-limiting toxicity.</td>
</tr>
<tr>
<td></td>
<td>In monotherapy: Severe diarrhoea was observed in 20% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 14% have a severe diarrhoea. The median time of onset of the first liquid stool was on day 5 after the infusion.</td>
</tr>
<tr>
<td></td>
<td>In combination therapy: Severe diarrhoea was observed in 13.1% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9% have a severe diarrhoea. Uncommon cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically (Clostridium difficile).</td>
</tr>
<tr>
<td></td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>In monotherapy: Nausea and vomiting were severe in approximately 10% of patients treated with antiemetics.</td>
</tr>
<tr>
<td></td>
<td>In combination therapy: A lower incidence of severe nausea and vomiting was observed (2.1% and 2.8% of patients respectively).</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Episodes of dehydration commonly associated with diarrhoea and/or vomiting have been reported. Infrequent cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting.</td>
</tr>
<tr>
<td></td>
<td>Other gastrointestinal disorders</td>
</tr>
</tbody>
</table>
|                    | Constipation has been observed:
|                    | • in monotherapy: in less than 10% of patients (monotherapy) |
|                    | • in combination therapy: 3.4% of patients |
|                    | Infrequent cases of intestinal obstruction, ileus, or gastrointestinal haemorrhage and rare cases of colitis, including typhilitis, ischemic and ulcerative colitis, were reported. Rare cases of intestinal perforation were reported. Other mild |
| Renal and Urological Disorders | Doxorubicin may impart a red colour to urine particularly to the first specimen passed after the injection and patients should be advised that this is no cause for alarm. |
| Reproductive System and Breast Disorders | Amenorrhoea, oligospermia and azospermia. |
| General Disorders and Administration Site Conditions | The risk of thrombophlebitis at the injection site may be minimised by following the procedure for administration recommended above. A stinging or burning sensation at the site of administration signifies a small degree of extravasation and the infusion should be stopped and re-started in another vein. Fever, malaise, asthenia and chills. |
| Investigations | ECG abnormalities |

Table 3 shows the undesirable effects listed within the product labelling for irinotecan.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea (occurring more than 24 hours after administration) is a dose-limiting toxicity.</td>
</tr>
<tr>
<td></td>
<td>In combination therapy: Severe diarrhoea was observed in 78.7% of patients and was severe (neutrophil count &lt; 500 cells/mm³) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count below 1,000 cells/mm³ including 7.6% with a neutrophil count &lt; 500 cells/mm³. Total recovery was usually reached by day 22.</td>
</tr>
<tr>
<td></td>
<td>Fever with severe neutropenia was reported in 6.2% of patients and in 1.7% of cycles. Infectious episodes occurred in about 10.3% of patients (2.5% of cycles) and were associated with severe neutropenia in about 5.3% of patients (1.1% of cycles), and resulted in death in 2 cases.</td>
</tr>
<tr>
<td></td>
<td>Anaemia was reported in about 58.7% of patients (8% with haemoglobin &lt; 8 g/dl and 0.9% with haemoglobin &lt; 6.5 g/dl).</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (&lt; 100,000 cells/mm³) was observed in 7.4% of patients and 1.8% of cycles with 0.9% with platelets count ≤ 50,000 cells/mm³ and 0.2% of cycles. Nearly all the patients showed a recovery by day 22.</td>
</tr>
<tr>
<td></td>
<td>In combination therapy: Neutropenia was observed in 82.5% of patients and was severe (neutrophil count &lt; 500 cells/mm³) in 9.8% of patients. Of the evaluable cycles, 67.3% had a neutrophil count below 1,000 cells/mm³ including 2.7% with a neutrophil count &lt; 500 cells/mm³. Total recovery was usually reached within 7-8 days.</td>
</tr>
<tr>
<td></td>
<td>Fever with severe neutropenia was reported in 3.4% of patients and in 0.9% of cycles. Infectious episodes occurred in about 2% of patients (0.5% of cycles) and were associated with severe neutropenia in about 2.1% of patients (0.5% of cycles), and resulted in death in 1 case.</td>
</tr>
<tr>
<td></td>
<td>Anaemia was reported in 97.2% of patients (2.1% with haemoglobin &lt; 8 g/dl).</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (&lt; 100,000 cells/mm³) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (&lt; 50,000 cells/mm³) has been observed.</td>
</tr>
<tr>
<td></td>
<td>One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported in the post-marketing experience.</td>
</tr>
<tr>
<td>Infection and infestation</td>
<td>Infrequent cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced sepsis.</td>
</tr>
<tr>
<td>General disorders and infusion site reactions</td>
<td>Acute cholinergic syndrome</td>
</tr>
</tbody>
</table>
|                    | Severe transient acute cholinergic syndrome was observed in 9% of patients treated in monotherapy. The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chill, malaise, dizziness, visual disturbances, myosis, lacrimation and increased salivation occurring during or
Table 3: Undesirable Effects listed within the product labelling for irinotecan

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>within the first 24 hours after the infusion. These symptoms disappear after atropine administration (see « Special warnings and precautions for use » from SmPC of the corresponding drug). Asthenia was severe in less than 10 % of patients treated in monotherapy and in 6.2 % of patients treated in combination therapy. The causal relationship to irinotecan treatment has not been clearly established. Fever in the absence of infection and without concomitant severe neutropenia, occurred in 12 % of patients treated in monotherapy and in 6.2 % of patients treated in combination therapy. Mild infusion site reactions have been reported although uncommonly.</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td>Rare cases of hypertension during or following the infusion have been reported.</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects such as dyspnoea have been reported.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia was very common and reversible. Mild cutaneous reactions have been reported although uncommonly.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon mild allergy reactions and rare cases of anaphylactic/anaphylactoid reactions have been reported.</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>Early effects such as muscular contraction or cramps and paresthesia have been reported.</td>
</tr>
<tr>
<td>Laboratory tests:</td>
<td>In monotherapy: Transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed in 9.2%, 8.1% and 1.8% of the patients, respectively, in the absence of progressive liver metastasis. Transient and mild to moderate increases of serum levels of creatinine have been observed in 7.3% of the patients. In combination therapy: transient serum levels (grades 1 and 2) of either SGPT, SGOT, alkaline phosphatase or bilirubin were observed in 15%, 11%, 11% and 10% of the patients, respectively, in the absence of progressive liver metastasis. Transient grade 3 were observed in 0%, 0% and 1% of the patients, respectively. No grade 4 was observed. Increases of amylase and/or lipase have been very rarely reported. Rare cases of hypokalemia and hypotension mostly related with diarrhea and vomiting have been reported.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>There have been very rare postmarketing reports of transient speech disorders associated with irinotecan infusions.</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Irinotecan has been rarely associated with thromboembolic events (pulmonary embolism, venous thrombosis, and arterial thromboembolism) in patients presenting with multiple risk factors in addition to the underlying neoplasm.</td>
</tr>
</tbody>
</table>

**CHOICE OF BEAD SIZE:**

Smaller DC Bead™ sizes, either 100-300µm or DC BeadMT™ (70-150µm), are recommended for standard HCC procedures or for the treatment of liver metastases from colorectal cancer. This choice is based on the demonstration that such small particles are delivered inside the tumour or in close proximity to the tumour margin and thus are ideal for drug delivery and precise embolisation. However, individual patient and tumour characteristics, particularly the identification of arteriovenous shunting, should be taken into account when the safety of the treatment and the choice of DC Bead™/DC BeadMT™ size are determined. In the case of significant arterioportal or hepatic venous shunting, embolisation of the shunt with gelfoam pledgets is recommended before proceeding with administration of DC Bead™/DC BeadMT™. Angiographic confirmation that the shunt is no longer present must be obtained before DC Bead™/DC BeadMT™ injection can be performed, and a larger bead size may be preferred.

**TREATMENT AND RETREATMENT:**

**Treatment and Retreatment of HCC with doxorubicin-loaded DC Bead™/DC BeadMT™**

In patients with residual viable tumour - including partial response, stable disease, and progressive disease according to mRECIST - further treatment with DC Bead™/DC BeadMT™ (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 tumours, 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.

**Treatment and Retreatment of liver metastases from colorectal cancer with irinotecan- loaded DC Bead™/DC BeadMT™**

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™/DC BeadMT™ 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™/DC BeadMT™**

- To minimise the risk of microbiological contamination DC Bead™/DC BeadMT™ should be prepared under controlled aseptic conditions. As the preparation and loading conditions of DC Bead™/DC BeadMT™ are outside of the manufacturer’s control, once the vial has been pierced, the allocation of a shelf life of 4 hours when stored at room temperature or 24 hours if stored in a refrigerator at 2-8°C is the responsibility of the user.

- When removing the vial from outer packaging, visually inspect for breakage or sharp edges prior to use.

- Use appropriate protective clothing and hygiene measures.

**Drug loading instructions**

DC Bead™ and DC BeadMT™ are suitable for loading with doxorubicin or irinotecan.

**WARNING:** Due to the cytotoxicity of the chemotherapeutic agents (that may be chosen by the prescriber for use with the device based on an informed clinical assessment) and requirement for aseptic preparation, the procedure is hazardous to staff and should only be undertaken by trained personnel in appropriate, validated aseptic facilities.

Liposomal formulations of doxorubicin are not suitable for loading into DC Bead™/DC BeadMT™.

**Select drug to be used**

1. Handle the drug according to manufacturer’s guidelines. The following drugs may be used:
   - Doxorubicin powder: reconstitute with sterile water for injection (not saline) to achieve a concentration of 25mg/ml
   - Doxorubicin solution (2 mg/ml)
   - Irinotecan solution (20 mg/ml)

**Transfer DC Bead™/DC BeadMT™**

2. Remove the flip cap from the DC Bead™/DC BeadMT™ vaginal applicator but do not remove the metal ring securing the stopper.

3. Transfer the contents of the vial into a 20ml syringe using a transfer
device or needle (minimum size 18G/ >0.84mm inner diameter). When using doxorubicin solution (2 mg/ml) use a 50 ml syringe.
4. Expel excess physiological buffered saline (packing solution) to leave only DC Bead™/DC BeadM™ in the syringe. For this hold the syringe in an upright position to let the microspheres settle on the plunger. Ensure DC Bead™/DC BeadM™ microspheres are settled in the syringe prior to removing packing solution to avoid loss of product.

**Load DC Bead™/DC BeadM™**
5. Transfer the required volume of doxorubicin / irinotecan solution into the syringe containing the DC Bead™/DC BeadM™. Do not exceed the recommended maximum loading dose:
   - 37.5mg of doxorubicin per 1ml of DC Bead™/DC BeadM™ (equivalent to 75mg per vial).
   - 50mg of irinotecan per 1ml of DC Bead™/DC BeadM™ (equivalent to 100mg per vial).
6. Cap the syringe.
7. Gently agitate the DC Bead™/DC BeadM™ by inverting the syringe ten times to ensure the beads are mobilised and exposed to the solution. Agitate
   - Doxorubicin (25 mg/ml) loading: every 30 minutes until loading time is complete.
   - Doxorubicin (2 mg/ml) loading: every hour until loading is complete. For 500-700µm DC Bead™ agitate every 4 hours for the first 8 hours and then at 24 hours.
   - Irinotecan (20 mg/ml) loading: every 30 minutes until loading time is complete.
8. Store and agitate the DC Bead™/DC BeadM™ according to the loading table below.

<table>
<thead>
<tr>
<th>Bead size</th>
<th>70-150µm</th>
<th>100-300µm</th>
<th>300-500µm</th>
<th>500-700µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading times (doxorubicin 25mg/ml)</td>
<td>30 minutes</td>
<td>45 minutes</td>
<td>90 minutes</td>
<td>90 minutes</td>
</tr>
<tr>
<td>Loading times (doxorubicin 2mg/ml)</td>
<td>3 hours</td>
<td>4 hours</td>
<td>8 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Loading times (irinotecan 20mg/ml)</td>
<td>60 minutes</td>
<td>60 minutes</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

DC Bead™/DC BeadM™ should be loaded at room temperature (for doxorubicin 25mg/ml and irinotecan 20mg/ml).

For doxorubicin2 mg/ml DC Bead™/DC BeadM™ should be loaded at 2 – 8°C. For loading outside the isolator please use adequate microbiological protection as per hospital guidance (e.g. double bagged containment).

**Completion of loading**

**Warning:** On completion of the loading time for doxorubicin, the supernatant will retain a light red tinge; this light colouring is normal and not an indication of incomplete loading. Strict adherence to the loading instructions, process and loading times will ensure ≥98% loading. The product should not be used in the event of an intensely red opaque coloured supernatant, as this is an indication of inadequate loading or excess added doxorubicin.

9. When loading time is complete expel the excess loading solution into a suitable container containing a total volume of 2ml of loaded DC Bead™/DC BeadM™. For this hold the syringe in an upright position to let the microspheres settle on the plunger. Ensure DC Bead™/DC BeadM™ microspheres are settled in the syringe prior to removing the depleted drug solution to avoid loss of product. 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.).

10. Cap the syringe and store until required (refer to Table 5).

**DC BeadM™**

<table>
<thead>
<tr>
<th>Product</th>
<th>Size range</th>
<th>Size range (Doxorubicin loaded)</th>
<th>Size range (Irinotecan loaded)</th>
<th>Catheter (Distal diam.)</th>
<th>Catheter (Inner diam.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC BeadM™ 70-150µm</td>
<td>70 – 170µm*</td>
<td>70 – 170µm*</td>
<td>70 170µm*</td>
<td>≥ 2.0 Fr</td>
<td>≥ 0.19” (≥0.49mm)</td>
</tr>
<tr>
<td>DC BeadM™ 100-300µm</td>
<td>70 – 340µm*</td>
<td>70 – 340µm*</td>
<td>70 340µm*</td>
<td>≥ 2.4 Fr</td>
<td>≥ 0.22” (≥0.54mm)</td>
</tr>
<tr>
<td>DC BeadM™ 300-500µm</td>
<td>250 – 550µm*</td>
<td>230 – 440µm (&lt;10% outside 250 – 550µm)</td>
<td>250 – 550µm*</td>
<td>≥ 2.4 Fr</td>
<td>≥ 0.22” (≥0.54mm)</td>
</tr>
<tr>
<td>DC BeadM™ 500-700µm</td>
<td>450 – 750µm*</td>
<td>370 – 525µm (&lt;60% outside 450 – 750µm)</td>
<td>n.a.</td>
<td>≥ 2.7 Fr</td>
<td>≥ 0.25” (≥0.65mm)</td>
</tr>
</tbody>
</table>

* Expected bead size range, < 5% beads outside this range. ** when loaded max. drug doses (Doxorubicin 37.5 mg/ml, Irinotecan 50 mg/ ml)

**Table 5: Chemical and physical stability of drug-loaded DC Bead™/DC BeadM™**

**Mixing with contrast agents**
- Take care to generate proper suspension of the DC Bead™/DC BeadM™ in the contrast medium to enhance distribution during injection. 10-20ml of non-ionic contrast medium can be added per vial of DC Bead™/DC BeadM™. Mixing of beads and contrast agent is performed via syringe to syringe mixing using a connector.
- The use of Visipaque (lodixanol) with irinotecan-loaded DC Bead™/DC BeadM™ is contraindicated as irinotecan might be eluted to a significant extent into the solution when using Visipaque.
- If the beads float, sterile water for injection can be added to the suspension mixture or if the beads sink, additional non-ionic contrast medium should be added. The suspension formation can be visually observed within seconds.

**DELIVERY INSTRUCTIONS:**
- Carefully evaluate the vascular network associated with the lesion using high resolution imaging prior to beginning the embolisation procedure.
- DC Bead™ is available in a range of sizes. Care should be taken to choose the appropriate size of DC Bead™ or to choose DC BeadM™ to best match the pathology (i.e., vascular target/vessel size) and provide the desired clinical outcome.
- Choose a delivery catheter based on the size of the target vessel.

**Table 4: DC Bead™/DC BeadM™ loading times based on achieving ≥98% loading of the respective drug.**

**Table 6: Size ranges and catheter compatibility**

**Prior to and during delivery, ensure visually that the beads are in suspension.**
- Introduce the delivery catheter into the target vessel according to standard techniques. Position the catheter tip as close as possible to the tumour feeding vessels to avoid inadvertent occlusion of normal vessels.
- Slowly inject DC Bead™/DC BeadM™ 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 Bead™/DC BeadM™ still within the catheter lumen.
- Following the applicable local standard practice and the cytotoxic drug manufacturers’ guidelines to dispose of cytotoxics and clinical waste, discard any unused DC Bead™/DC BeadM™.
REFERENCES: