Embozene TANDEM™
(Microspheres for Embolization)

* Embozene TANDEM™ is available outside of the US only
Embozene® Color-Advanced Microspheres

- Precise size calibration
- Structural integrity and compressibility
- Stable suspension
- Biocompatibility
PRODUCT INFORMATION

• Embozene TANDEM Microspheres for Embolization combine the precision and ease of use customers have always appreciated in Embozene® Microspheres with full integration of drugs*.

• Due to the design characteristics, Embozene TANDEM Microspheres may be loaded with up to 50 mg/ml microspheres:
  – **Doxorubicin-HCl** for local, controlled, sustained dose elution to targeted tumor sites such as *hepatocellular carcinoma (HCC)* after embolization.
  – **Irinotecan-HCl** for local, controlled, sustained dose elution to targeted tumor sites such as *metastatic colorectal cancer (mCRC)* after embolization.

* Embozene TANDEM microspheres are indicated for embolization according to the IFU. They may be loaded with a drug to elute a local, controlled, sustained dose of said drug to targeted tumor sites after embolization. Loading of drug should be under a physician’s direction, choice and responsibility, based on type and dose of drug most beneficial to the patient.
DRUG-LOADING AND RELEASING MECHANISM

Ion-exchange mechanism

[Debutchicin] or [Irubicin]

**DEB-TACE non-ionic CA**
drug releasing via ion exchange

or

**Irino-tecan**
DRUG-ELUTING MICROSPHERES

Advantages

• Higher potential for standardized procedure versus cTACE\(^1\)
• cTACE improves survival compared to BSC\(^2\)
• Reduced systemic exposure to Doxorubicin versus cTACE\(^3\)
• Reduced liver toxicity versus cTACE\(^4\)
• Reduced drug-related side effects versus cTACE\(^4\)
• Higher objective response for more advanced disease\(^4\)
• Higher degree of necrosis\(^5\) and longer time-to-progression\(^6\) versus TAE
• Reduced systemic exposure to Irinotecan, higher and prolonged tumor drug concentration, and higher necrosis versus IA and IV\(^7\)
• Improved survival versus FOLFIRI\(^8\)

Limitation

• Survival benefit for treatment of HCC\(^9\)

1. Lewis 2012
4. Lammer 2010
5. Lewis 2006, Nicolini 2010
6. Malagari 2010
7. Rao 2012
8. Aliberti 2011
9. Lammer 2010 vs Dhanasekaran 2010
DRUG-ELUTING MICROSPHERES
TREND TO SMALLER SIZE

Advantages of small over large microspheres

• Better/deeper tumor penetration$^{1,3}$
• Higher degree of necrosis$^2$
• Improved drug coverage$^3$

→ next step: small, tightly size-calibrated drug eluting microsphere (≤ 100 µm)

**TAE**

- large bandwidth calibrated particles
  - wide size range

**mb-TAE**

- close bandwidth calibrated particles
  - close size range

**Embozene**

- 40 μm ± 10 μm
- 100 μm ± 25 μm
- 250 μm ± 50 μm
- 400 μm ± 50 μm
- 500 μm ± 50 μm
- 700 μm ± 50 μm
- 900 μm ± 75 μm

Slide from Prof. Orsi (Milan, Italy)
PRODUCT INFORMATION

• TANDEM Microspheres Reference Numbers:

<table>
<thead>
<tr>
<th>Size</th>
<th>2mL Syringe</th>
<th>3mL Syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 ± 10 µm</td>
<td>10420-TS0</td>
<td>10430-TS0</td>
</tr>
<tr>
<td>75 ± 15 µm</td>
<td>10720-TS0</td>
<td>10730-TS0</td>
</tr>
<tr>
<td>100 ± 25 µm</td>
<td>11020-TS0</td>
<td>11030-TS0</td>
</tr>
</tbody>
</table>

Embozene TANDEM is not currently available in the US.

To order Embozene TANDEM, please contact your local CeloNova representative, or visit [www.celonova.com](http://www.celonova.com)
Contrast agent strategy

- Use only non-ionic contrast agent

<table>
<thead>
<tr>
<th>Type</th>
<th>Brand Name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodixanol</td>
<td>- Visipaque</td>
</tr>
<tr>
<td>Iohexol</td>
<td>- Accupaque</td>
</tr>
<tr>
<td></td>
<td>- Omnipaque</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>- Ioparimo</td>
</tr>
<tr>
<td></td>
<td>- Isovue</td>
</tr>
<tr>
<td></td>
<td>- Solutrast</td>
</tr>
<tr>
<td>Iopromide</td>
<td>- Ultravist</td>
</tr>
<tr>
<td>Ioversol</td>
<td>- Optiject</td>
</tr>
<tr>
<td></td>
<td>- Optiray</td>
</tr>
</tbody>
</table>

- Use 5 mls of contrast per 1 ml of TANDEM microspheres:
  - 2 ml TANDEM syringe: 10 mls of contrast agent
  - 3 ml TANDEM syringe: 15 mls of contrast agent
DRUG-LOADING PROCEDURE

1. **Doxorubicin (powder):** dilute with WFI to get 20 mg/ml

2. **Remove excess of transport solution**

3. **Aspire Doxorubicin solution (20 mg/ml)**

4. **Shake according to IFU (at least **every 5 mins for the first 20 mins**)**

   **Remove excess of transport solution**

• Easier drug-loading procedure

• High drug-loading efficiency
# DRUG-LOADING TIMES

## Loading of Doxorubicin

<table>
<thead>
<tr>
<th>Bead size</th>
<th>Doxorubicin Concentration [mg/ml]</th>
<th>Loading Time [min]</th>
<th>Loaded Drug [%]</th>
<th>Post-Loading Size Change [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANDEM™ 40 µm</td>
<td>50</td>
<td>60</td>
<td>98 ± 2</td>
<td>≤ 5</td>
</tr>
<tr>
<td>TANDEM™ 75 µm</td>
<td>50</td>
<td>60</td>
<td>98 ± 2</td>
<td>≤ 5</td>
</tr>
<tr>
<td>TANDEM™ 100 µm</td>
<td>50</td>
<td>60</td>
<td>98 ± 2</td>
<td>≤ 5</td>
</tr>
<tr>
<td>Competitor (100-300 µm)</td>
<td>37.5</td>
<td>60</td>
<td>98 ± 3</td>
<td>≤ 20*</td>
</tr>
</tbody>
</table>

* for 25 mg/ml

## Loading of Irinotecan

<table>
<thead>
<tr>
<th>Bead size</th>
<th>Irinotecan Concentration [mg/ml]</th>
<th>Loading Time [min]</th>
<th>Loaded Drug [%]</th>
<th>Post-Loading Size Change [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANDEM™ 40 µm</td>
<td>50</td>
<td>30</td>
<td>98 ± 2</td>
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<td>≤ 5</td>
</tr>
<tr>
<td>TANDEM™ 100 µm</td>
<td>50</td>
<td>30</td>
<td>98 ± 2</td>
<td>≤ 5</td>
</tr>
<tr>
<td>Competitor (100-300 µm)</td>
<td>50</td>
<td>120</td>
<td>98 ± 3</td>
<td>≤ 30</td>
</tr>
<tr>
<td>Competitor (70-150 µm)</td>
<td>50</td>
<td>120</td>
<td>98 ± 3</td>
<td>≤ 30</td>
</tr>
</tbody>
</table>

Tables represent typical measured values, not specifications.
TANDEM™: TIGHT CALIBRATION AND SIZE STABILITY

<table>
<thead>
<tr>
<th>Microsphere</th>
<th>Doxorubicin [mg/ml microspheres]</th>
<th>Irinotecan [mg/ml microspheres]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embozene TANDEM™</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Competitor (100-300 µm)</td>
<td>37.5</td>
<td>50</td>
</tr>
<tr>
<td>Competitor (70-150 µm)</td>
<td>-</td>
<td>50</td>
</tr>
</tbody>
</table>

Figures represent typical measured values, not specifications.
SIZE STABILITY MATTERS

Model assumptions

- Packing density identical for unloaded and drug-loaded microspheres
- All microspheres have uniform size

Total volume reduction due to size decrease during drug-loading

Theoretical calculation
NUMBER OF MICROSPHERES

Number of microspheres per ml in correlation to their size

<table>
<thead>
<tr>
<th>Microsphere</th>
<th>Microspheres per ml [10^6]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embozene TANDEM™ 40 µm</td>
<td>21</td>
</tr>
<tr>
<td>Embozene TANDEM™ 75 µm</td>
<td>4</td>
</tr>
<tr>
<td>Embozene TANDEM™ 100 µm</td>
<td>1.7</td>
</tr>
<tr>
<td>Competitor (100-300 µm)</td>
<td>0.1*</td>
</tr>
<tr>
<td>Competitor (70-150 µm)</td>
<td>0.65*</td>
</tr>
</tbody>
</table>

*from competitors homepage

Packing density 70%

Typical measured values, not specifications
Release profiles of Irinotecan-loaded DEB (50 mg/ml microspheres); release monitored in process via UV-VIS spectroscopy at 37°C in SOTAX CE-1 elution system using isotonic medium, 5 ml/min flow rate.

Typical measured values, not specifications

European Oncology & Haematology, 2012 (in press)
## DRUG-RELEASE TIMES

### Release of Irinotecan

<table>
<thead>
<tr>
<th>Bead size</th>
<th>Irinotecan Concentration [mg/ml]</th>
<th>Time to release 25 mg Irinotecan [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANDEM™ 40 µm</td>
<td>49 ± 1</td>
<td>1</td>
</tr>
<tr>
<td>TANDEM™ 75 µm</td>
<td>49 ± 1</td>
<td>0.5</td>
</tr>
<tr>
<td>TANDEM™ 100 µm</td>
<td>49 ± 1</td>
<td>0.5</td>
</tr>
<tr>
<td>Competitor (100-300 µm)</td>
<td>49 ± 1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Competitor (70-150 µm)</td>
<td>49 ± 1.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Typical measured values, not specifications.
## DRUG-RELEASE TIMES

### Release of Doxorubicin

<table>
<thead>
<tr>
<th>Bead size</th>
<th>Doxorubicin Concentration [mg/ml]</th>
<th>Time to Release 10 mg Doxorubicin [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANDEM™ 40 µm</td>
<td>49 ± 1</td>
<td>3</td>
</tr>
<tr>
<td>TANDEM™ 75 µm</td>
<td>49 ± 1</td>
<td>3</td>
</tr>
<tr>
<td>TANDEM™ 100 µm</td>
<td>49 ± 1</td>
<td>3</td>
</tr>
<tr>
<td>Competitor (100-300 µm)</td>
<td>36.5 ± 1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Competitor (500-700 µm)</td>
<td>36.5 ± 1.5</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Small drug-eluting microspheres cause higher degree of necrosis\(^1,2,4\)
Large drug-eluting microspheres release slower\(^1,3\)
Large drug-eluting microspheres cause lower systemic drug levels\(^1\)
Large drug-eluting microspheres cause higher drug tissue concentration\(^4\)

Embozene TANDEM combines benefits of small microspheres with slower drug release.

Typical measured values, not specifications

Because of the higher drug loading capacity and the offering of 3 ml syringes, TANDEM will be more cost efficient for the hospital.

Example: a patient needs a dose of 150 mg of Doxorubicin
- TANDEM loads the drug faster, saving time and money
- TANDEM is capable of delivering 150 mg with one 3 ml syringe
- TANDEM can load 33% more drug in a 2 ml syringe

<table>
<thead>
<tr>
<th></th>
<th>Competition</th>
<th>TANDEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum drug loading capacity per 2 ml vial or syringe</td>
<td>75 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Maximum drug loading capacity per 3 ml vial or syringe</td>
<td>N/A</td>
<td>150 mg</td>
</tr>
<tr>
<td>Maximum drug loading capacity per 4 ml vial or syringe</td>
<td>150 mg (need 2 x 2 ml vials)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
TANDEM KEY FEATURES

• Can load doxorubicin and irinotecan faster and easier
  – Save time for the pharmacy (up to 90 minutes for loading irinotecan)

• Can load more drugs: up to 50 mg/ml microspheres
  – Load 150 mg of drug in one 3 ml syringe

• Drugs release more slowly
  – May reduce systemic side effects

• Microspheres do not change in size after drug loading
  – Easy passage through microcatheters
  – Ideal for targeted drug delivery near the tumor site
VALUE PROPOSITION

TANDEM Microspheres are cost efficient and beneficial for:

- **The Hospital:**
  - Capable of delivering drugs up to 150 mg with one 3 ml syringe
  - Capable of delivering more drugs with a 2 ml syringe

- **The Pharmacy:**
  - Easier drug loading, which saves time (up to 90 minutes faster for irinotecan and up to 60 minutes faster for doxorubicin)

- **The Physician:**
  - Choice between 2 ml and 3 ml volumes (no need to use multiple vials or syringes during the same procedure)
  - Ease of use (better fit through microcatheters)
  - Targeted embolizations (Tight calibration, less size changes after drug loading)

- **The Patient**
  - TANDEM Microspheres have a slower and more controlled drug release, which may result in fewer systemic effects and providing a higher level of patient care
TANDEM™ POSITIONING

Precision

• Targeted drug delivery with tightly calibrated microspheres and super-selective TACE

• Controlled and precise drug delivery and release at tumor site

• Microsphere size remains stable during drug loading and storage: typical size change less than 5%
TANDEM: TIGHT CALIBRATION AND SIZE STABILITY

→ Tight size-calibration decreases risk of premature vessel occlusion

Scale bar: 100 µm
TANDEM POSITIONING

Efficiency
- Deliver up to 150 mg of Doxorubicin-HCl or Irinotecan-HCl with one 3 ml syringe
- Fast drug loading times with superior drug loading capacity up to 50 mg/ml microspheres
- Controlled drug release rates for optimal localized drug delivery

Flexibility
- Available in three sizes (40 µm, 75 µm and 100 µm)
- Available in two volumes (2 ml & 3 ml syringes)
- Ideal for passage through micro catheters
TANDEM POSITIONING

Safety

• Color coded labels for easy recognition of microsphere sizes

• Slow and controlled drug release times may result in fewer systemic side effects
SUMMARY

Embozene TANDEM offers
• Small sizes
• Tight size calibration
• Size stability
• Fast drug-loading with high loading capacity
• Slow and controlled drug release

Embozene TANDEM is designed to
• Enable super-selective embolization
• Penetrate deeper into the tumor micro-vasculature
• Reduce systemic toxicity
• Improve drug coverage
• Increase tumor kill