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October 16th, 2012

Re: Use of Onyx® Liquid Embolic System (LES)

Dear International Onyx® LES Users,

On June 28, 2012, the U.S. Food and Drug Administration (FDA) issued a Safety Communication (enclosed) to inform physicians and patients about the risk of catheter entrapment associated with the use of Onyx® Liquid Embolic System (LES).

In light of the differences between the clinical and regulatory status of Onyx® in the USA and international markets a similar field safety communication (in regions receiving non-USA versions of Onyx) could be misleading and confusing:

- In the USA, the Onyx® Liquid Embolic System is indicated to block blood flow in brain Arteriovenous Malformations (AVMs) before their surgical removal. Onyx is not intended to be a long-term implant. In international markets, the Onyx® Liquid Embolic System is indicated to block blood flow in brain AVMs and there is usually no surgical removal of the AVM after the procedure.
- The ev3 Apollo microcatheter with a detachable tip that is marketed internationally has been specifically designed for use with Onyx® and minimizes the risk of complications in case of catheter entrapment. This catheter is not yet approved for use in the USA.

Covidien has collaborated with the FDA on the catheter entrapment issue and submitted and received approval for specific changes to the USA Instructions for Use (IFU) for Onyx®.

These changes provide additional warnings regarding potential complications associated with catheter entrapment during delivery of Onyx® LES. These adverse events were not observed in the pivotal clinical study, but there have been infrequent incidences of catheter entrapment reported during commercial use of the product since July 2005.

The Onyx educational programs detail these potential complications, and it is important to be aware of these potential complications during selection of patients for treatment with Onyx® LES.

In addition to the changes to the USA IFU, we are also considering updates to the international.

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Specific changes being considered to the international IFU are detailed below.

1) The following complications in red are being added to the "Potential Complications" section of the Onyx® LES IFU:
   - Catheter entrapment
   - Catheter rupture
   - Device migration and cast movement
   - Hemorrhagic complications related to attempts to remove entrapped catheter

2) The following content in red is being added to the "Warnings" section of the Onyx® LES IFU:

   - Do not allow more than 1 cm of Onyx® LES to reflux back over catheter tip. Angioarchitecture, vasospasm, excessive Onyx® LES reflux or prolonged injection time may result in difficult catheter removal and potential entrapment. Excessive force to remove an entrapped catheter may cause serious intracranial hemorrhage. The long-term effects of an entrapped catheter that is left in a patient are unknown, but potentially could include clot formation, infection or catheter migration.

3) The following content in red is being added to the "Precautions" section of the Onyx® LES IFU:

   Difficult catheter removal or catheter entrapment may be caused by any of the following:
   - Angioarchitecture: very distal bAVM fed by afferent, lengthened, small or tortuous pedicles
   - Vasospasm
   - Reflux
   - Injection time

   To reduce the risk of catheter entrapment, carefully select catheter placement and manage reflux to minimize the factors listed above.

The above changes highlighted in red are in the process of being considered for the International IFUs delivered with Onyx® LES.

Covidien Regulatory Affairs will work with the local Regulatory Officials in your country to determine the strategy for these IFU changes if deemed necesssary.

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If you have any questions, please contact me or one of the individuals listed below:

Thank you,

16 OCT 2012

Laura Heaton
Sr. Manager, Regulatory Affairs
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Date