Onyx® Liquid Embolic System
Onyx® HD-500

ev3®
THE ENDOVASCULAR COMPANY

Instructions for Use

DRAFT 5-7-07

INSTRUCTIONS FOR USE

US05830178, US05785642, US05755658, US05695480, US05667767, US05958444 and Other US and Foreign Patents Pending

It is important to read the instructions for use with careful attention to warnings prior to using this product.

Onyx® and DMSO are sterile (dry heat) and non-pyrogenic.

Syringes and the interface device are sterile and non-pyrogenic.
This device is intended for SINGLE USE ONLY. **DO NOT RESTERILIZE AND/OR REUSE.**

Humanitarian Device. Authorized by Federal law for use in the intracranial, saccular, sidewall aneurysms that present with a wide neck (≥ 4 mm) or with a dome-to-neck ratio < 2 that are not amenable to treatment with surgical clipping. The effectiveness of this device for this use has not been demonstrated.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

- This device should be used only by physicians with a thorough understanding of angiography and percutaneous neurointerventional procedures.
- Onyx must be used with appropriately designed DMSO compatible micro catheters, balloon catheters and syringes.

DESCRIPTION

Onyx® Liquid Embolic System (Onyx® HD-500, Model 105-8101-500)

Onyx® Liquid Embolic System (Onyx® HD-500), referred to as Onyx®, is a non-adhesive liquid embolic agent comprised of EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide) and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. The Onyx® HD-500 System includes a 1.5 ml vial of Onyx® HD-500, a 1.5 ml vial of DMSO, one DMSO 1ml delivery syringe, one threaded Onyx® delivery syringe and an interface device. The following DMSO compatible accessory devices are required for use with the Onyx® HD-500 System:

- HyperForm™ or HyperGlide™ or Equinox Occlusion Balloon Systems (104-4000 Series)
- Rebar-14 Micro Catheter (105-5080-153)

Onyx® for the embolization of aneurysms is available in one product formulation, Onyx® HD-500 (9.4% EVOH by weight).

PRINCIPLE OF OPERATION

Onyx® is delivered by slow controlled injection through a micro catheter into the aneurysm under fluoroscopic control. The DMSO solvent dissipates into the blood, causing the EVOH copolymer and suspended tantalum to precipitate *in situ* into a

spongy, coherent embolus. Onyx® immediately forms a skin as the polymeric embolus solidifies from the outside to the inside, while filling more distally in the aneurysm. Final solidification of this material occurs within five minutes.

INDICATIONS FOR USE

Onyx® Liquid Embolic System (Onyx® HD-500) is indicated for treatment of intracranial, saccular, sidewall aneurysms that present with a wide neck (≥ 4 mm) or with a dome-to-neck ratio < 2 that are not amenable to treatment with surgical clipping.

CONTRAINDICATIONS

The use of the Onyx® Liquid Embolic System (Onyx® HD-500) is contraindicated when any of the following conditions exist:

- When optimal catheter placement is not possible.
- When vasospasm stops blood flow.

WARNINGS

- The safety and effectiveness of Onyx® as a long term implant has not been established.
- Due to the liquid nature of Onyx®, consideration should be given to the potential risk of Onyx® leakage into critical arteries in close proximity to the target aneurysm or originating from within the aneurysm sac.
- Rates of device protrusion into the parent vessel and parent artery occlusion (PAO) for patients treated with Onyx® were highest in Part 1 of the clinical study during which parent artery remodeling with Onyx® was permitted and an antiplatelet regimen was not used for all patients. Do not use Onyx® to remodel the parent artery and use the antiplatelet regimen recommended in the Directions for Use.
- Performing embolization to occlude blood vessels is a high risk procedure. This device should be used only by physicians with neurointerventional training and a thorough knowledge of the pathology to be treated, angiographic techniques, and super-selective embolization.
- Animal studies have shown that a rapid injection of DMSO into the vasculature may lead to vasospasm and/or angionecrosis. Do not exceed maximum injection rate as specified in the Directions for Use (step 14).
- Animal experimentation has shown that when Onyx® escapes outside the vascular space, as might occur if the vessel wall is compromised, a subacute inflammatory response to the material may occur. Increased intracranial pressure due to unresorbed Onyx® material in this space may cause tissue damage. Users should exercise extra caution when infusing the device.

- DMSO can initiate the liberation of histamine and there has been an occasional hypersensitivity reaction observed with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient being treated for interstitial cystitis. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

- DMSO may interact with other embolic agents, such as polymer coated coils, e.g., gel coatings and suture material coated coils. If unsure of a potential chemical interaction, contact ev3 or embolic agent manufacturer.

- Therapeutic embolization should not be performed when high blood flow precludes safe infusion of the embolic agent.

- Failure to continuously mix Onyx® for the required time may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery (see Directions for Use below). Inject Onyx® immediately after mixing. If Onyx® injection is delayed, tantalum settling can occur within the syringe resulting in poor visualization of Onyx® during injection.

- Adequate fluoroscopic visualization must be maintained during Onyx® delivery or non-target vessel embolization may result. If visualization is lost at any time during the embolization procedure, **HALT** Onyx® delivery until adequate visualization is re-established.

- Premature solidification of Onyx® may occur if the micro catheter luer contacts any amount of saline, blood or contrast.

- After using a micro catheter with Onyx®, do not attempt to clear or inject any material through it. Such attempts may lead to the creation of an embolus and/or embolization of an unintended area.

- Onyx® injection quantity and rate described in step 14 are maximum amounts. Depending on the remaining aneurysm volume, the amount and rate should be reduced. Due to residual pressure in the micro catheter, a small amount of Onyx® will exit catheter after injection has stopped. Failure to monitor the injection carefully may result in overfilling leading to protrusion or migration of Onyx® into the parent artery.

- Failure to place catheter as shown (see Directions for Use below, step 4) may result in an extraction force exceeding the tensile strength of catheter. Do not allow more than 1 cm of Onyx® to reflux back over catheter tip. Excessive Onyx® reflux may result in difficult catheter removal.

- If flow through the micro catheter becomes restricted when using the Onyx®, do not attempt to clear the micro catheter by high-pressure infusion. Remove the

catheter and replace it with a new one. Use of excessive pressure may result in catheter rupture.

- If Onyx® does not appear after 2 full revolutions of the threaded syringe handle, stop injection and replace catheter. Excessive pressure may result in catheter rupture. Testing has shown that over-pressurization and rupture can occur if only a volume of 0.05 ml of Onyx® is injected and is not visualized exiting the catheter tip.

- Failure to aspirate syringe and wait ten minutes prior to retrieval of micro catheter, may result in fragmentation of Onyx®.

PRECAUTIONS

- The safety and effectiveness has not been studied in the following patient populations:
    - Pregnant and nursing women.
    - Individuals less than 18 years old.
    - Patients with intracranial stents and/or coils.
    - Individuals with significant impairment of liver and kidney function.

- Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

- A garlic-like taste may be noted by the patient with use of Onyx® due to the DMSO component. This taste may last several hours. An odor on the breath and skin may be present.

- Inspect product packaging prior to use. Do not use if sterile barrier is open or damaged.

- Use prior to expiration date.

- Verify that the catheters and accessories (see directions for use) used in direct contact with the Onyx® polymer are clean and compatible with the material and do not trigger polymerization or degrade with contact. Use only ev3 Neurovascular micro catheters indicated for use in the neurovasculature, e.g., Rebar and ev3 Neurovascular syringes. Other micro catheters or syringes may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degradation. Refer to the Warnings and Directions for Use sections.

TRAINING

Serious, including fatal, consequences could result with the use of the Onyx® Liquid Embolic System (Onyx® HD-500) without adequate training. Contact your ev3 Neurovascular sales representative for information on training courses.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Table 1 identifies the adverse events observed in a clinical study conducted to evaluate the safety and probable benefit of the Onyx® HD-500 System. The events are listed by frequency of occurrence. The clinical investigation enrolled a total of 66 patients whose aneurysms were treated with Onyx®. During the study, the clinical protocol was revised to ensure the appropriate application of Onyx® and to require consistent treatment regimens across investigational sites. Safety information is presented for all patients in the study (Table 1). Due to the revision of the protocol, adverse events specific to the neurological health of the patients is presented in Table 2 as Study Part 1 and Part 2 data. Information is presented on all patients through the 6 month follow-up endpoint (for full discussion of the clinical information, see Summary of Clinical Studies).

Table 1. Incidence of Complications

Complication	Onyx® Patients (n=66)		
	Events	**Pts**	**%**
Neurological, e.g., headache, visual impairment, ataxia/unsteady gait	126	51	(77.3%)
Gastrointestinal, e.g., nausea/vomiting, constipation, heartburn	46	31	(47.0%)
Vascular Complications, e.g., access site pain, hematoma, and bleeding	38	29	(43.9%)
Pulmonary/Respiratory, e.g., pneumonia, respiratory failure, COPD exacerbation	30	20	(30.3%)
Musculoskeletal, e.g., joint pain, misc. somatic pain, neck/back pain	28	21	(31.8%)
Dermatological. e.g., skin bruising, urticaria/itching, alopecia	18	14	(21.2%)
Cardiac, e.g., increased blood pressure, decreased blood pressure, arrthymias/bradycardia	18	13	(19.7%)
Metabolic, e.g., electrolyte change	9	9	(13.6%)
Constitutional, e.g. anemia, dehydration	13	11	(16.7%)
Vasospasm	9	8	(12.1%)
Protrusion in Parent Vessel *	15	15	(22.7%)
Stroke - Ischemic	16	15	(22.7%)
Urogenital	10	10	(15.2%)
Other – Misc.	8	8	(12.1%)
PAO – Partial *	7	7	(10.6%)
Distal Embolic Events	2	2	(3.0%)
PAO – Complete *	8	8	(12.1%)
Death	3	3	(4.5%)
PAO – Stent Induced	1	1	(1.5%)
Perforations / Dissections	5	5	(7.6%)
Stroke - Hemorrhagic	3	3	(4.5%)
Hematological	2	2	(3.0%)

The rates of device protrusion into the parent vessel and parent artery occlusion (PAO) for patients treated with Onyx® were highest in Part 1 of the IDE study during which parent artery remodeling with Onyx® was permitted and an antiplatelet regimen was not utilized for all patients. The clinical protocol was revised to dis-allow parent artery remodeling, and to include a required anti-platelet regimen before, during and after

embolization in Part 2. The rate of Onyx® protrusion into the parent artery was 10/38 (26.3%) for patients in Part 1 of the study and 5/28 (17.9%) for patients in Part 2. The incidence of parent artery occlusion was 7/38 (18.4%) in Part 1 of the study and 1/28 (3.6%) for patients in Part 2 (Table 2). The incidence of ischemic stroke was noted to be diminished post-revision of the protocol. In Part 1 of the study, the incidence of ischemic stroke was 11/38 (28.9%) whereas in Part 2, 4/28 patients (14.3%) were observed to have an event.

Table 2. Incidence of Complications

Complication	Onyx Patients					
	Part 1 n =38			Part 2 n =28		
	Events	Pts	%	Events	Pts	%
Neurological, e.g., headache, visual impairment, ataxia/unsteady gait	75	30	78.9	51	21	75
Vasospasm	3	3	7.9	6	5	17.9
Protrusion in Parent Vessel *	10	10	26.3	5	5	17.9
Stroke - Ischemic	12	11	28.9	4	4	14.3
PAO – Partial *	5	5	13.2	2	2	7.1
Distal Embolic Events	0	0	0	2	2	7.1
PAO – Complete *	7	7	18.4	1	1	3.6
PAO – Stent Induced	0	0	0	1	1	3.6
Perforations / Dissections	5	5	13.2	0	0	0.0
Stroke - Hemorrhagic	3	3	7.9	0	0	0.0

The incidence of neuro-specific adverse events observed for 44 patients enrolled under the same protocol and treated with GDC coils was:

- Neurological 34 (77.2%)
- Vasospasm: 4 (9.1%)
- Protrusion in parent vessel: 4 (9.1%)
- Stroke (ischemic): 4 (9.1%)
- PAO (partial): 1 (2.3%)
- PAO (complete): 1 (2.3%)
- Stroke (hemorrhagic): 2 (4.5%)

- Two patients (4.5%) treated with GDC coils died during the study.

SUMMARY OF CLINICAL STUDIES

Clinical data was presented from three studies conducted in the U.S. and Europe that evaluated the safety and probable benefit of the Onyx® HD-500 System for use in difficult to treat intracranial aneurysms.

In the U.S. an Investigational Device Exemption (IDE) study comparing Onyx® to GDC coils was initiated to evaluate safety and effectiveness of embolization for intracranial aneurysms that, because of their morphology, location, or the patient's medical condition, were considered by the treating neurosurgical team to be either very high risk for management by traditional operative techniques or inoperable. The study enrolled a total of 110 patients with 66/110 aneurysms treated with Onyx®. The trial was a prospective multi-center study with randomization of patients to treatment with either Onyx® or GDC coils. The GDC coils were considered a reasonable reflection of contemporary procedures and practices for embolization of aneurysms and provided a baseline for comparison of patient outcome to Onyx® treated aneurysms. The primary effectiveness endpoint was six-month aneurysm occlusion ≥90% without retreatment. The primary safety endpoint was a six-month composite of morbidity and mortality as measured by neurological assessment of new or worsening of symptoms, or new neurological symptoms and deficits.

The trial was conducted in two parts due to inappropriate and un-intended use of the Onyx® material as a vasculature modeling agent in the first part of the trial. During Part 1 of the trial, a high incidence of partial to complete parent artery occlusions was reported (5/38 partial occlusion, 13.2%; 7/38 complete, 18.4%). These were generally attributable to, parent artery remodeling with Onyx® as well as inconsistent use of antiplatelet regimens. In Part 2, the protocol was revised to prohibit parent artery remodeling and to require an antiplatelet regimen. In addition, the selection criteria were modified so that only *de novo*, unruptured aneurysms with a maximum neck diameter of 10 mm were included. . Also, the primary endpoint was modified to be a composite of occlusion effectiveness and safety, i.e., ≥ 90% angiographic aneurysm occlusion at follow-up without a major adverse event (death, major stroke, SAH from the treated aneurysm) or retreatment. An additional forty patients were enrolled in Part 2 of the trial. The incidence of complete parent artery occlusion was 7/38 (18.4%) of Onyx® patients in Part 1 of the study and 1/28 (3.6%) of patients in Part 2. The incidence of Onyx® protrusion into the parent artery was 10/38 (26.3%) of patients in Part 1 of the study and 5/28 (17.9%) of patients in Part 2.

During Part 1 of the study, there was significant enrollment bias, i.e., aneurysm dome height and width were both statistically significantly greater for the Onyx-treated group. As noted above, the clinical protocol was thus revised to ensure a more balanced distribution of aneurysms between study groups. Maximal neck size was limited to 10 mm and only patients with *de novo* and unruptured aneurysms were enrolled. Review of aneurysm characteristics for both Part 1 and Part 2 study groups revealed that a significant portion met criteria that distinguished them as a feasible patient population for Humanitarian Use Designation (HUD). Clinical data from both study parts was

combined to evaluate the safety and probable benefit of Onyx for the treatment of wide-necked aneurysms.

No device, e.g., coil, particulate embolic agent, etc., is recognized as an effective treatment for wide-neck aneurysms, though coiling is performed by clinicians for this disease. Thus clinical data collected from treatment of patients with GDC coils was used as an indicator of the comparative safety and probable benefit of using Onyx in treating this group of difficult-to-treat aneurysms.

In addition, a similar cohort of patients with wide-neck aneurysms was treated with Onyx in the Cerebral Aneurysm Multicenter European Onyx Study (CAMEO). The CAMEO Study was initiated to collect safety and performance data for CE mark approval and commercialization in European countries. After approval, the study was continued as a post market Registry to collect data on physician experience using the Onyx® system. CAMEO physicians selected patients for the Study with aneurysms that:

a) Were likely to be difficult to treat or presented high risk for conventional coil techniques or neurosurgical clip placement

b) Had recurred following previous coil embolization, or

c) Had failed to respond to prior surgical or endovascular treatment.

Patients diagnosed with ruptured or unruptured intracranial aneurysms were enrolled in the study based on investigator experience and assessment of the aneurysm size and morphology as suitable for treatment with Onyx®. Patients were evaluated post embolization, and at 3, 6 and 12 months post procedure. The primary effectiveness endpoint was a measure of angiographic occlusion of the aneurysm. The primary safety endpoint was a measure of patient morbidity and mortality. Clinical endpoint measures included a standard assessment of neurological functions and patient outcome determined after initial treatment and at each scheduled follow-up period.

For both the IDE and CAMEO studies, endpoint success rates are presented in the following tables. Both simple and composite endpoint rates are summarized. A simple effectiveness endpoint was based on $\geq$ 90% angiographic aneurysm occlusion at follow-up. The composite endpoint was based on $\geq$ 90% angiographic aneurysm occlusion at follow-up without a major adverse event (death, major stroke, SAH from the treated aneurysm) or retreatment.

Table 3 summarizes study endpoints for all aneurysms treated in the CAMEO and US IDE (Parts 1 and 2 combined) sponsored studies. The analyses include HUD and non-HUD treated aneurysms.

Table 3. Comparison of Endpoint Success Rates for Aneurysms

Endpoint Analysis	CAMEO Study	U.S. IDE Trial Aneurysms	
	Onyx® Treated (n=100)	Onyx® Treated (n=66)	GDC Treated (n=44)
Intent-to-Treat Efficacy Endpoint ≥ 90% Occlusion at Follow-up	--	41/59 (69.5%)	24/40 (60.0%)
Intent-to-Treat Composite Endpoint ≥ 90% Occlusion w/o Major Adverse Event	--	38/59 (64.4%)	21/40 (52.5%)
Per Protocol Efficacy Endpoint ≥ 90% Occlusion at Follow-up	64/70 (91.4%)	40/49 (81.6%)	23/36 (63.9%)
Per Protocol Composite Endpoint ≥ 90% Occlusion w/o Major Adverse Event	56/70 (80%)	37/49 (75.5%)	20/36 (55.6%)
Follow-up Period	12 Months	6 Months	6 Months

1. Intent-to-treat analysis excludes late screen failure and no assessment patient population.
2. Per protocol analysis excludes late screen failure, no assessment, failed to treat and crossover patient population.
3. Intent-to-Treat data is not available for the CAMEO study.

Table 4 summarizes study endpoints for all aneurysms meeting the HUD criteria in the CAMEO and US IDE sponsored studies, i.e., intracranial, saccular, sidewall aneurysms that present with a wide neck (≥ 4 mm) or with a dome-to-neck ratio < 2 that are not amenable to treatment with surgical clipping.

Table 4. Comparison of Endpoint Success Rates for HUD Aneurysms

Endpoint Analysis	CAMEO Study	U.S. IDE Trial Aneurysms	
	Onyx® Treated (n=63)	Onyx® Treated (n=53)	GDC Treated (n=34)
Intent-to-Treat Efficacy Endpoint ≥ 90% Occlusion at Follow-up	--	33/49 (67.3%)	21/32 (65.6%)
Intent-to-Treat Composite Endpoint ≥ 90% Occlusion w/o Major Adverse Event	--	31/49 (63.3%)	19/32 (59.4%)
Per Protocol Efficacy Endpoint ≥ 90% Occlusion at Follow-up	51/63 (81.0%)	32/40 (80.0%)	20/29 (69.0%)
Composite Endpoint ≥ 90% Occlusion w/o Major Adverse Event	43/63 (68.3%)	30/40 (75.0%)	18/29 (62.1%)
Follow-up Period	12 Months	6 Months	6 Months

1. Intent-to-treat analysis excludes late screen failure and no assessment patient population.
2. Per protocol analysis excludes late screen failure, no assessment, failed to treat and crossover patient population.
3. Intent-to-Treat data is not available for the CAMEO study.

Additional experience has been reported for 100 consecutive aneurysms treated with Onyx® in 94 patients (1). The initial selection criteria included aneurysms that were difficult to treat with conventional endovascular techniques or surgical clipping, had recurred following prior coil embolization, or had failed prior surgical or endovascular treatment. Later, the criteria were modified to exclude any ICA aneurysm in which a vessel originating from the aneurysm, was at the origin of the anterior choroidal artery or

posterior communicating artery, and was too large for the protecting balloon to seal the aneurysm.

Patients were evaluated clinically with Modified Rankin Scores (mRS). At discharge, 83/94 (88.3%) patients had unchanged or improved mRS, while 8 (8.5%) patients had worsened mRS. There were six (6.4%) transient neurological adverse events which resolved completely. Procedure- or device-related permanent neurological morbidity was observed in eight (8.5%) patients. These included visual loss, ophthalmoplegia and worsening of cranial nerve palsies, and one case of right MCA infarct. Delayed spontaneous asymptomatic occlusion of the parent vessel occurred in two patients at 6 month follow-up.

HOW SUPPLIED

The Onyx® Liquid Embolic System (Onyx® HD-500) is available in one product formulation, Onyx® HD-500 (20% EVOH).

STORAGE

Store Onyx® and DMSO in a cool dry place. Prior to use, maintain product temperature between 19° and 24°C. If product freezes due to exposure to colder temperatures, thaw at room temperature before use.

DIRECTIONS FOR USE

WARNING: Verify that adequate sedation is used throughout the embolization procedure. Insufficient sedation may result in patient discomfort or movement. Patient movement during embolic agent injection may result in embolization of an unintended vessel.

WARNING: To diminish the incidence of complications, antiplatelet therapy is recommended. The following regimen was required during clinical studies:

	ASA	**Plavix**
Pre-Procedure (3 days)	Per Institutional Practice / as required per patient	
During Embolization	ACT ≥ 2X Baseline	
Post Procedure (Bolus at completion unless previously administered)	325 mg	450 mg
Follow-up (3 months)	325 mg qd	75 mg qd

1. **Dry heat[2] Onyx® vial at 70° C for 5 minutes** then shake 20 minutes using an Onyx® mixer[3] at a setting of 8. After mixing, heat for a minimum of 5 minutes prior to aspiration.

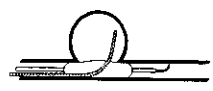
WARNING: Failure to continuously mix Onyx® for the required time may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery.

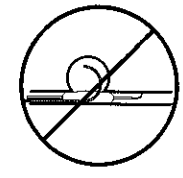
WARNING: Use only ev3 Neurovascular micro catheters indicated for use in the neurovasculature, e.g., Rebar, and 1 ml syringes. Other micro catheters or syringes may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degradation.

2. Prepare patient using femoral access catheterization technique. Continuously flush and heparinize per institutional protocol. Use guiding catheter(s) of sufficient inner diameter to accommodate both the continuous flush and devices used in the procedure.

3. Insert balloon catheter to bridge the neck of the aneurysm.

4. Insert micro catheter through the aneurysm inflow zone and place the tip of the catheter in upper 1/3 of aneurysm sac. Ensure the catheter tip does not loop back over center (see diagram below).





WARNING: Failure to place catheter as shown may result in extraction force exceeding tensile strength of catheter.

5. Confirm micro catheter placement in upper third (1/3) of aneurysm sac with a slow contrast injection through the micro catheter.

6. Inflate balloon to confirm aneurysm neck is bridged with a slow, low volume contrast injection through the micro catheter. Note volume of balloon inflation for use during the embolization.

7. With the balloon deflated, use syringe to flush contrast from micro catheter with 5 ml of saline. Leave the syringe connected until ready to attach DMSO 1ml syringe.

8. Fill micro catheter dead space by aspirating approximately 0.8 ml of sterile DMSO into the DMSO 1 ml syringe. Inject the DMSO into the micro catheter in sufficient volume to just fill the catheter dead space at a rate not greater than 0.3 ml/min. Refer to micro catheter label for dead space volume.

9. Ensure that the Onyx® has been mixed per step 1. Fill an ev3 Neurovascular Onyx® 1 ml threaded syringe with Onyx® through a 15 gauge needle. Pull plunger back until non-threaded area is exposed. Then slide the white Quick-Stop clip over until it hits the tab. Push plunger forward until threads engage. Remove 15 gauge needle and connect the interface device to the syringe. Turn syringe knob

to inject Onyx® through the interface device and remove air. After the Onyx® syringe is prepared, remove the DMSO syringe and overfill and wash the luer hub with the balance of the DMSO.

WARNING: Premature solidification of Onyx® may occur if micro catheter luer contacts saline, blood or contrast of any amount.

10. ***Immediately*** connect the Onyx® threaded syringe/interface device to the micro catheter hub, making sure there is no air in the hub during the connection.

Note: The threaded syringe generates a tactile click for each full revolution. Each full revolution is equal to 0.015 ml.

Note: The Quick-Stop clip must be engaged to start the Onyx® injection (see figure 1). The Quick-Stop clip can be disengaged to immediately stop the flow of Onyx® (see figure 2).

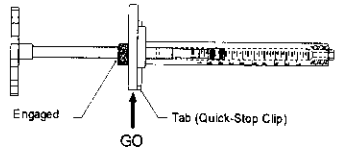


Figure 1

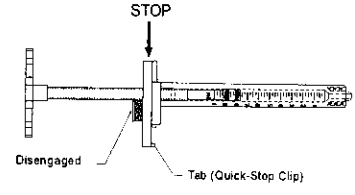


Figure 2

11. Per the table below, inject Onyx® into micro catheter at a steady rate not to exceed 0.10 ml/min. (balloon deflated). This will expel the DMSO from the micro catheter and fill the majority of catheter with Onyx.

Micro Catheter		Onyx® Priming Volume
Rebar-14	105-5080-153	0.20 ml maximum

WARNING: Animal studies have shown that a rapid injection of DMSO into the vasculature may lead to vasospasm and/or angionecrosis.

12. Wait one minute for DMSO to disperse from aneurysm sac.

Note: Repeated angiographic subtraction enhances Onyx® visualization.

13. Inflate balloon to same volume as determined in step 6.

14. Inject Onyx® through the micro catheter at a rate not to exceed 0.10 ml/min. On the first injection, create a small Onyx ball at the catheter tip. Then inject Onyx® per the table below.

WARNING: Never exceed maximum injection rate, injection volume or injection time.

Micro Catheter	Onyx® Kit	Maximum Onyx® Injection Volume	Maximum Injection Time
Rebar-14 105-5080-153	Onyx® HD 500 105-8101-500	0.20 ml	2 minutes

WARNING: If Onyx does not appear after 2 full revolutions of the threaded syringe handle, stop injection and replace catheter. Excessive pressure may result in catheter rupture.

WARNING: After using a micro catheter or syringe with Onyx®, do not attempt to clear or re-use the device. Attempts to clear catheter may lead to embolization of unintended areas.

WARNING: If flow through the micro catheter becomes restricted when using the Onyx® Liquid Embolic System (Onyx® HD-500), do not attempt to clear the micro catheter by high-pressure infusion. Remove the catheter and replace it with a new one. Use of excessive pressure may result in catheter rupture.

15. Allow the balloon to stay inflated after injection per the minimum solidification time below. This will permit the Onyx® to solidify. Then completely deflate balloon to reestablish perfusion.

Onyx® Kit		Minimum Solidification Time after Injection
Onyx HD 500	105-8101-500	3 minutes

Note: Repeated angiographic subtraction enhances Onyx® visualization.

16. Repeat steps 14-16 until fill of aneurysm sac is complete.

17. Upon completion of aneurysm embolization, aspirate Onyx® syringe at least 0.20 ml. Aspiration creates a vacuum in the micro catheter and prevents inadvertent injection of Onyx during catheter removal.

18. Allow 10 minutes for Onyx® solidification with the balloon deflated.

WARNING: Failure to aspirate syringe and wait 10 minutes prior to retrieval of micro catheter, may result in fragmentation of Onyx®.

19. Inflate balloon to approximately 75% of volume determined in step 6. Loosen Tuohy Borst, remove slack from micro catheter, then with a quick pull separate the micro catheter from the Onyx® mass.

    - Remove all slack from the catheter by putting a few centimeters of traction on the catheter to create a slight tension in the catheter system.
    - Firmly hold the catheter and then pull it using a quick wrist snap motion (from left to right) 10 – 15 centimeters to remove the catheter from the Onyx® cast.

20. Deflate and remove balloon system.

References

1. Cekirge SH, Saatci I, Ozturk HM, Cil B, Arat A, Mawad M, Ergungor F, Belen D, Er U, Turk S, Bavbek M, Sekerci Z, Beskonakli E, Ozcan OE, Ozgen T. Late angiographic and clinical follow-up results of 100 consecutive aneurysms treated with Onyx reconstruction: largest single-center experience. Neuroradiology DOI 10.1007/s00234-005-007-6, 2005.
2. Barnstead/Thermolyne Model No(s): DB117315PRO, 120V, DB117310-33PRO, 240V.
3. Scientific Industries Genie 2, Model No(s). 120V SI-0240, 240V SI-0251, Vial Attachment No. OA-0570-010

ev3®
THE ENDOVASCULAR COMPANY

PATIENT INFORMATION BROCHURE

Facts about the

Onyx® Liquid Embolic System

for the treatment of Intracranial Aneurysms

www.ev3.net

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Definition of Medical Terms

Anesthesia (general or local)

Anesthesia means the loss of sensations, such as pain, temperature or touch. General anesthesia means you will be given a drug or gas to make you unconscious during a procedure. Local anesthesia, brought about by an anesthetic, means the loss of sensation limited to a specific area of the body.

Angiography

Angiography is a procedure used to help diagnose and treat blood vessel disease. A special type of liquid that can be seen with x-ray machines is injected into the blood vessel. X-ray machines can then be used to see the blood vessels, diagnose disease, and aid the doctor during treatment of the disease.

Aneurysm

A cerebral aneurysm is a pouch or protrusion from a blood vessel. Aneurysms may occurrin various locations in the brain. They appear in a variety of shapes and sizes. Aneurysms are classified by size: Small: less than 10mm in dome width, Large: 10-25mm; and Giant: greater than 25mm. As well aneurysms can be classified by the width of the neck (or opening): some aneurysms are referred to as "wide necked." Aneurysms can occur in certain shapes – such as "sidewall" aneurysms occurring directly from the side of a vessel, or such as "bifurcation" aneurysms that may occur where to vessel bifurcate.

Bifurcation/bifurcate

Aneurysms may have 2 branches or divisions. The aneurysm may be described as having a point of forking, or having a bifurcation.

Embolization Device (Material)

An embolization device is a material placed within an aneurysm to occlude or block blood flow into the aneurysm. Embolization procedures are performed to minimize the risk of rupture. The most common devices for the embolization of aneurysms are detachable coils. Coils have unique properties that make them more or less suitable for a particular embolization procedure.

Hypersensitivity (allergies)

Hypersensitivity is a condition in which there is an exaggerated response by the body to a material or medication. The reaction is commonly referred to as an allergic reaction. The reaction can be very serious and may increase in severity with each successive exposure to the medication.

Micro Catheter

A micro catheter is long, thin, tube-like device which is placed in the blood vessel to deliver various diagnostic and therapeutic materials. During an embolization procedure, a micro catheter is used to deliver the Onyx material into the aneurysm.

Balloon

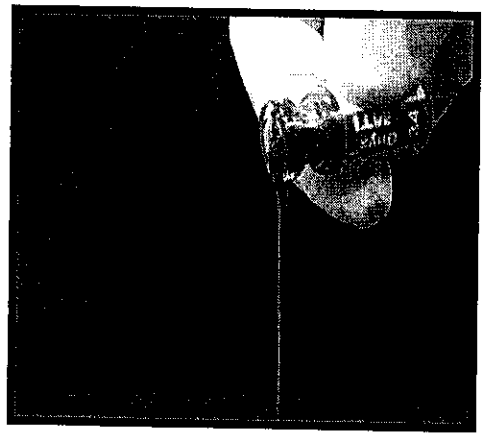
A balloon is similar to a micro catheter. It is a long tube-like device which is placed along the opening of the aneurysm. During the embolization and delivery of Onyx, the balloon is inflated to temporarily seal the neck of the aneurysm to assist the proper placement of the Onyx material. The balloon is then removed after the procedure is complete.

Purpose of the Onyx Liquid Embolic System (LES)

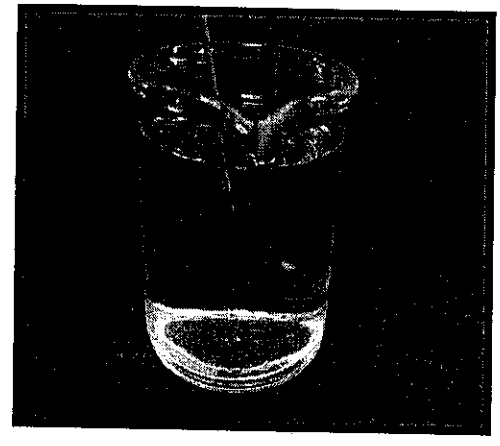
The Onyx material is intended for the embolization of large and giant, wide-necked aneurysms. The material may offer a benefit in particular cases that other devices may not. For these reasons, your physician has recommended embolization using Onyx.

Description of the Onyx LES Device

Onyx is the trade name for a liquid polymeric embolization device manufactured by ev3 Neurovascular. The liquid Onyx is delivered through a micro catheter selectively placed within an aneurysm. Hardening of the Onyx begins immediately when it comes into contact with bodily fluids, such as blood.



Onyx in liquid form



Onyx precipitation in saline

When the Onyx LES Device Should Not Be Used

There are some contraindications for the Onyx LES System. The Onyx LES System is contraindicated:

- when your physician cannot optimally position the catheter to deliver the Onyx, and/or
- when your physician feels you may not tolerate the procedure.

However, many factors can potentially affect the outcome of a procedure. The safety of Onyx has not been established for use if you are::

- Pregnant or nursing
- A young child
- Diagnosed with significant impairment of liver and kidney function.

Be sure to inform your doctor of any known allergies or hypersensitivity to any drug, food or environmental condition.

Risks and Benefits

To achieve FDA clearance under a Humanitarian Use Designation, ev3 Neurovascular submitted clinical and technical information to the FDA for review. These data included results from international clinical experience as well as US clinical data from a company sponsored clinical trial.

Potential Risks

The embolization material Onyx could unexpectedly enter the parent vessel from where the aneurysm arises. Although rare in occurrence, in some cases the material could travel into the blood vessel and possibly create an undesirable blockage of the blood vessel or a smaller blood vessel. Temporary or permanent disability, bleeding, or stroke could result from blockage of vital blood vessels supplying the brain or the spinal cord. Stroke or bleeding could result in muscle weakening or paralysis, numbness, hearing problems, sensory problems, visual disturbances or defects, mental or physical disability, speech problems, or death.

You may experience pain, headache, nausea, infection or other symptoms of illness or temporary discomfort during and after the procedure. Medications may be required for these symptoms.

Use of Onyx to treat your aneurysm may present risks to you which are currently unknown or unforeseeable. The degree of the specific risks of embolization varies from patient to patient depending upon the type and location of the aneurysm and other risk factors related to your condition.

Many of the risks for this procedure are also reported for procedures with other embolization devices. If you do not understand any of the potential risks, ask your doctor to explain them to you.

Potential Benefits

- The Onyx embolization material is expected to stop or reduce blood flow into the aneurysm. It is anticipated that embolization of the aneurysm may help in correcting or lessening of some or all of your symptoms.

Expectations of the Device and the Procedure Associated with the Device

Preparing for the procedure, the procedure itself, and post-procedure care are essentially the same as for most embolization materials. There are no special or unique procedures associated with the use of Onyx for treating aneurysms.

Pre-Procedure Exams

You will undergo a series of exams and diagnostic procedures to fully assess the size, shape, and location of your aneurysm. Your doctor will use this information to plan the most appropriate course of treatment. Exams and procedures will generally include the following:

- Medical history review
- Physical examination
- Blood tests
- Neurological examination
- Imaging (CT, MRI)
- Angiography

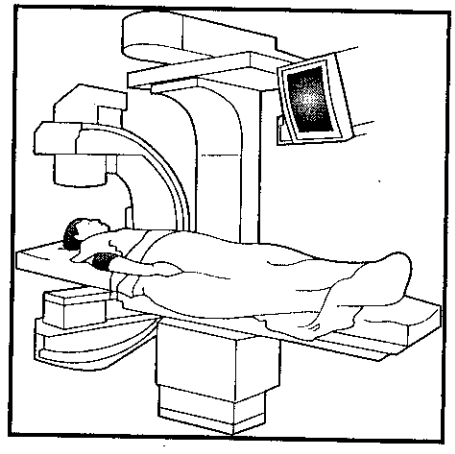
Pre-Procedure Medications

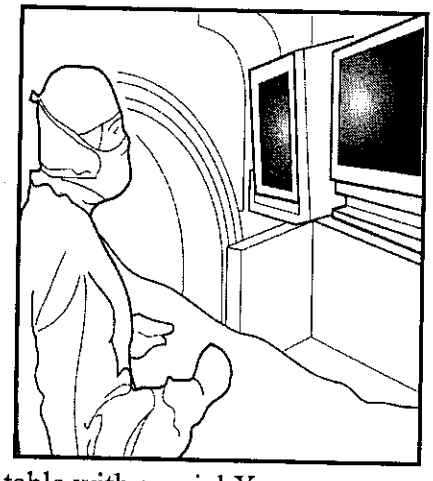
Your doctor may require you to prepare for the procedure a few days in advance. Preparation may include taking aspirin or anti-clotting medication for 2-3 days before the procedure. Additional medications may be prescribed by your doctor depending on your general health and other medications you are taking.

Embolization Procedure

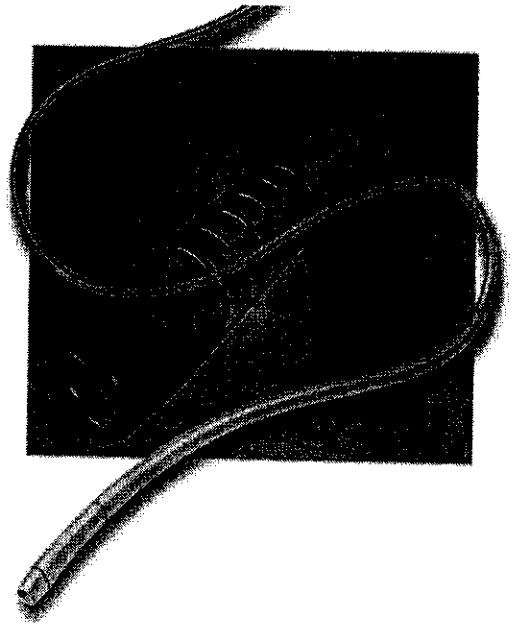
The procedure may be done under local or general anesthesia. Because patients must remain still for long periods of time, general anesthesia is usually preferred. Your doctor will determine the best and safest method for treating your aneurysm.

The actual embolization procedure can take a few hours . Time is taken to place the micro catheter into the aneurysm. Your doctor will try to fill the aneurysm completely with Onyx so no blood flow enters the aneurysm space.

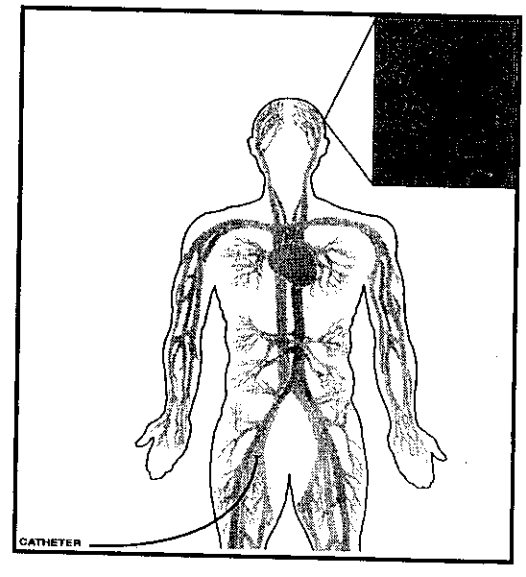




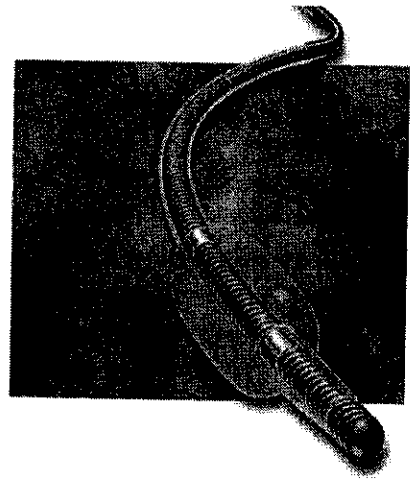
In the neuro angiography suite, the patient lies on a table with special X-ray and monitoring equipment that allows the physician to navigate catheters to the aneurysm for embolization.

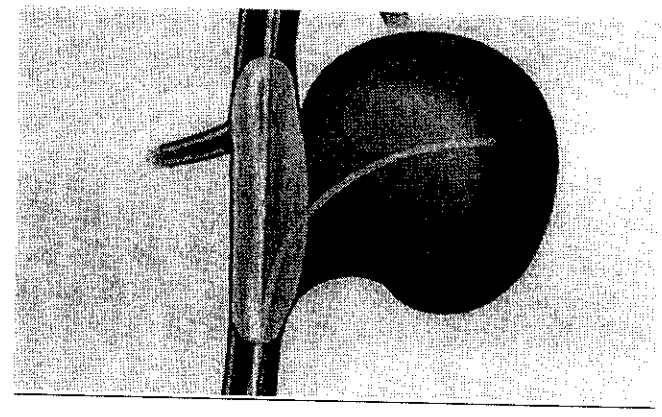


A small catheter (tube) is used for delivery of Onyx into the aneurysm.

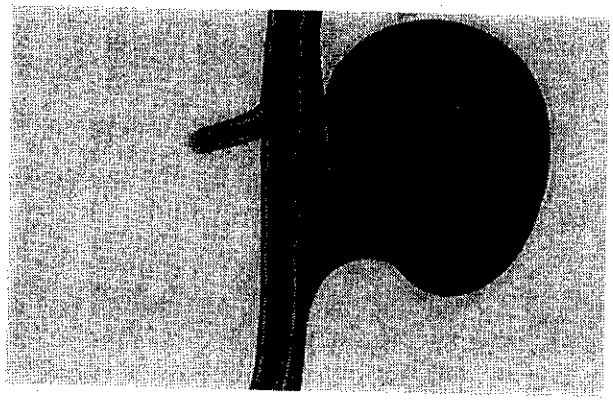


The Onyx delivery catheter is inserted through an artery in the upper leg. The catheter is pushed gently through the artery to the aneurysm site.





After the tip of the catheter is placed within the aneurysm, where Onyx can be delivered, a small catheter with a balloon at the tip is positioned along side the aneurysm to seal the opening during the delivery of Onyx into the aneurysm.



After the Onyx material has been injected into the aneurysm, the balloon catheter and Onyx delivery catheters are removed.

Post-Procedure Care

After the procedure is complete, you will be moved to a recovery room. You will likely experience some pain and tenderness in the groin area where the micro catheter was inserted into your blood vessel. Additionally, many patients have reported headache and nausea, as well as a strong garlic-like odor following procedures with Onyx. This is caused by metabolism of the DMSO solvent that was in the Onyx system. The odor usually disappears in 24-48 hours.

The Importance of Adhering to a Care Regimen

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There are no pre or post procedure care regimens specifically required for the Onyx material. However, your doctor(s) may prescribe certain medications before and after the embolization and surgical procedures. It is important for your safety to carefully follow the directions and medications prescribed by your doctor.

Additional Information

The following publications are available for additional information on the treatment of aneurysm and Onyx LES system.

1. Molyneux AJ, Cekirge S, Saatci I, Gal G. Cerebral Aneurysm Multicenter European Onyx (CAMEO) Trial: Results of a Prospective Observational Study in 20 European Centers. *AJNR* 25:39-51 January 2004
2. Late angiographic and clinical follow up results of 100 consecutive aneurysm treated with Onyx reconstruction: largest single-center experience by H.S. Cekirge, I. Saatci, B. Cil, A. Arat

User Assistance Information

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