SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name: Artificial Embolization Device

Device Trade Name: Onyx® Liquid Embolic System (Onyx® HD-500, Model 105-8101-500), Onyx®

Applicant's Name and Address: ev3 Neurovascular
9775 Toledo Way
Irvine, CA 92618
Establishment Registration No. 2029214

Humanitarian Device Exemption (HDE) Number:	H060003
Humanitarian Use Device (HUD) Designation Number:	HUD#: 02-0096
Date of Humanitarian Use Device (HUD) Designation:	November 19, 2003
Date(s) of Panel Recommendation:	None
Date of Notice of Approval to Applicant:	April 11, 2007

II. INDICATIONS FOR USE

Onyx® Liquid Embolic System (Onyx® HD-500) (hereinafter called the Onyx® HD-500 System and Onyx®) 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.

III. CONTRAINDICATIONS

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

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Onyx® HD-500 System labeling.

V. DEVICE DESCRIPTION

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)

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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Wide-neck aneurysms are difficult to treat both surgically and endovascularly. Surgical clipping may be difficult or impossible if there is no true aneurysm neck present. Endovascular therapy of wide neck aneurysms is sometimes limited to parent artery occlusion, if there is adequate collateral flow, or by a balloon-assisted technique. Currently, the most widely used treatment for wide neck aneurysms is placement of embolization coils within the aneurysm sac, but aneurysms with wide necks can not often structurally retain embolization coils and complications such as protrusion of the coil into the parent artery may occur. Recent availability of neurovascular stents through the Humanitarian Device Exemption regulatory provision has provided for an additional approach to aneurysm occlusion using endovascular techniques. Stent placement across the aneurysm neck maintains blood flow through the parent artery lumen while excluding the aneurysm sac. The stent serves to contain coils within the aneurysm space and prevent coil herniation into the parent vessel.

VII. MARKETING HISTORY

The Onyx® HD-500 System was first placed on the market in November 2000, in Europe with the CE mark for use in the treatment of aneurysms. Onyx® continues to be marketed throughout most European countries, Canada, Turkey, Australia, and some Latin American countries. Onyx® has not been withdrawn from the market in any country for any reason.

VIII. 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 Section X).

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

	Onyx Patients					
Complication	**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.

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

This section presents summaries of important preclinical studies in support of safety and probable benefit of the Onyx® HD-500 System. The following pre-clinical studies were conducted to ensure that the Onyx® is safe and potentially beneficial for its intended use: Mechanical/Chemical Tests, Biocompatibility Studies, Animal Studies, and Pre-trial Clinical Experience.

Mechanical/Chemical Tests

These tests (Table 3) cover the basic characterization of Onyx® as a solution and as an implanted precipitate, as well as compatibility with syringes/catheters and other embolic devices, such as coils.

Table 3. Mechanical/Chemical Tests

Study	Results and Conclusions
Tantalum Suspension	This test was performed to determine the minimum required shake time to mix and assure homogenous tantalum dispersion in Onyx®. The results showed that shaking the product for 20 minutes on an Onyx® mixer[1] at a setting of 8 will assure homogenous tantalum suspension. [1]Scientific Industries Genie 2, Model No(s). 120V SI-0240, 240V SI-0251, Vial Attachment No. OA-0570-010
Injection Pressures	Injection pressure determinations were conducted to verify that infusion pressures generated during delivery of Onyx® were within safe burst specification limits of the sponsor's Rebar micro-catheter. Onyx® was infused at 0.1 and 0.2 ml/min at 37°C via the Rebar micro catheter. The Onyx® IFU specifies a maximum Onyx® injection rate of 0.1 ml/min with the Rebar micro-catheter. The injection pressures were well below the burst pressure specification of the Rebar catheter.
Injection Run-on	Onyx® was assessed for its' run-on characteristics, i.e., when injection pressure is released, how far/long does the material continue to infuse. Onyx® was injected via a 0.018" lumen catheter to pre-determined points in horizontally placed catheters. Once injection was halted, any further migration of Onyx® was measured as a distance from the stop point over time. The distance Onyx® continued to "run" was measured over 10 minutes. The material continued to infuse at approximately .003 mL/minute over a 4 minute time interval for a total increase of approximately 12 µL. No significant amount more infusion was measured from 4 to 10 minutes.
Radiopacity	To assess radiopacity of Onyx®, the material was precipitated in 0.025" ID Silicone tubing and then compared to a metal guidewire. Imaging was performed in a cabinet X-ray system at 35.5 kV and 202 A, with image capturing software. The resultant images subjectively demonstrated adequate radiopacity when compared a stainless steel guidewire.
Onyx® Solidification Time	To determine Onyx® solidification time, Onyx® was precipitated in saline creating spherical Onyx® masses (approximately 3 mm in diameter). At controlled time intervals, the Onyx® spheres were compressed to determine when liquid could no longer be expelled from the mass. The results demonstrated that Onyx® spheres were solidified (no liquid expelled from the Onyx® mass) within 5 minutes.

Study	Results and Conclusions
Particulate Generation	The purpose of the study was to determine if Onyx®, under simulated fluid shear conditions, generates particles in its final precipitated form. Test samples were prepared by precipitating 3-4 mm spheres in vials containing saline. The vials were inverted 20 times, the spheres removed and the fluid analyzed with a spectrophotometer. The test results demonstrated that Onyx® particulate generation was less than the maximum allowable per U.S. Pharmacopeia (USP) XXV <788>.
Material Expansion	Several aliquots of Onyx® (8%) were precipitated in saline to determine expansion characteristics during and after precipitation. and for assessment of material mechanical properties (tensile strength and 180 degree folding characteristics). The diameter of the precipitates remained the same from day 1 – day 7 indicating that the material and its swelling capacity remained stable. The tensile strength test values indicate that the material had a range of 0.5-6.0 psi tensile strength with a general trend showing higher tensile test values for smaller diameter particles. No direct relationship between precipitate size and 180 degree bending ability was observed.
Material Adhesion	Silicone models of lateral wall aneurysms (approximate dimensions: parent artery 3 - 4mm ID; aneurysm neck 6 - 8mm; aneurysm diameter 8 - 10mm; aneurysm height 28 - 30mm) were embolized with Onyx® HD-500 per instructions for use. The force required to detach/remove the catheter from the Onyx® filled aneurysm model was measured with a force gauge attached to the catheter hub. Results demonstrated that the Rebar catheter removal force was significantly less than the catheter break force.
Effects of Radiation and Stability Onyx® Precipitates	To determine if radiation could cause a chemical alteration of the Onyx® material changing its biocompatibility profile or cause a degradative effect to the polymer, samples of Onyx® precipitates were exposed to 30 Gray of radiation and then aged at 55°C for 210 days (2 year equivalent). The samples were tested for biocompatibility, chemical stability, and physical integrity. Cytotoxicity, acute systemic toxicity, hemolysis, and pyrogenicity evaluations showed no evidence of toxicity, hemolytic activity or change in pyrogen content. Infrared Absorption Spectroscopy and Gel Permeation Chromatography evaluations showed nearly superimposable Infrared (IR) spectra and equivalent molecular weight determinations, respectively. The test results demonstrated that Onyx® was unaffected by radiation levels encountered during radiosurgery.
Device (Catheter and Syringe) Chemical Compatibility Testing	To determine if DMSO (the active solvent in Onyx®) degrades the supplied/recommended delivery devices (the Rebar Micro Catheters, Interface Device and the 1 mL syringes), chemical and functional performance of the delivery devices after exposure to DMSO was assessed. After initial infusion of DMSO through each delivery device, the DMSO-exposed catheters were assessed for static burst and tensile strength, and the syringes for peak force strength and visualization of gradations. The test results demonstrated that delivery device strength values (burst, tensile and peak force) and the visibility of the gradations did not degrade after extended DMSO exposure and were similar to non-DMSO exposed samples. The DMSO effluent was assessed via High Performance Liquid Chromatography (HPLC) for detection of chemicals potentially eluted from the delivery devices by the solvent. No additional peaks other than DMSO were detected demonstrating that the recommended ancillary delivery devices are chemically compatible with DMSO.

Study	Results and Conclusions
Adjunctive Device Compatibility (Coils and Glues)	Coil and cyanoacrylate-based embolization agents may be used in conjunction with Onyx®. Metal coils were incubated with DMSO to determine if the solvent could leach any chemical from the coils. HPLC evaluations revealed no leachates. The same coils were used together with Onyx® to perform an embolization of a simulated vessel. The target was occluded and no distal migration of Onyx® was observed. To assess for Onyx®/cyanoacrylate compatibility, a cyanoacrylate cast was first formed in a simulated fistula model. The embolic cast was then incubated with DMSO for 60 minutes. No migration of the embolic cast was observed (flow rate: 300 mL/min. Also, DMSO did not cause any cyanoacrylate embolic cast leaching/degradation as determined by HPLC analysis.
Sterilization Validation	Dry Heat sterilization of Onyx® and DMSO is performed and validated (ANSI/AAMI ST63:2002 - Sterilization of health care products – requirements for the development, validation and routine control of an industrial sterilization process for medical devices – dry heat) using a half cycle approach with BI indicators to achieve an SAL of 10^{-6}. Ethylene Oxide Sterilization of the packaged Syringes is performed and validated in accordance with ANSI/AAMI/ISO 11135-1994, Medical Sterilization - validation and routine control of ethylene oxide sterilization, using the Method C Overkill process in accordance with Annex A of the standard.
Package Integrity	The Onyx® HD-500 System was subjected to a Federal Express vibration and drop testing for packages 0 – 75 lbs according to ISTA 1A / D4169 following 4 days at –20°C, 29 days at 55°C and humidity less than 20% and 27 days at 55°C and 70-80% relative humidity. The test results demonstrated appropriate package integrity.
Sterile Product – DMSO and Onyx® sterile barrier	To demonstrate appropriate sterile barrier, aged vials (three years accelerated aging) were subjected to pressure leak testing and were tested for sterility. No leaks were observed, and all tested samples were sterile. Based on test results, the sterile barrier vial package system for DMSO and Onyx® is an effective sterile barrier.
Onyx® Real Time and Accelerated Aging	Stability of Onyx® was assessed by conducting accelerated and real time aging test protocols to support a 3-year product shelf life. The tests included the following evaluations: Leakage, Product Sterility, Cytotoxicity, Molecular Weight Distribution via GPC, Viscosity, Density, Precipitation and Extractables on Precipitation via GC/MS. Based on the testing results, Onyx® System met the necessary criteria for a 3-year shelf life.
DMSO Real Time and Accelerated Aging	The potential for the effects of aging on the performance of DMSO were evaluated by conducting accelerated and real time aging testing to support a 3-year product shelf life. The testing consisted of analysis for impurities, including dimethyl sulfone. There were no trends in the levels or types of impurities. Based on the testing results, DMSO met the necessary criteria for a 3-year shelf life.

Biocompatibility Studies

Biocompatibility studies were performed per ISO 10993-1, Biological evaluation of medical devices for permanent implants, blood contact (Table 4). Additional biocompatibility testing was performed per FDA's *Guidance on Biocompatibility Requirements for Long Term Neurological Implants.*

Table 4. Summary Table: ISO 10993-1 Biocompatibility Test Results

Test	Description	Results
Cytotoxicity	MEM Elution Test Evaluation – whole device Study results interpretation Assuming an Onyx flow rate of 0.1 ml/min (per IFU), dividing 0.1 mL/min by flow rates of 350 mL/min or 100 mL/min, the volumetric dilutions are 1/3500 and 1/1000, respectively. Therefore, the 1/4 non-cytotoxic result represents at least a 250-fold safety margin.	Dilution (response) Grade* 1:1 4, severe 1:2 3, moderate 1:4 0, none *tissue response severity is graded on a scale of 0-4
Cytotoxicity	MEM Elution Test Evaluation of DMSO Study results interpretation See Cytotoxicity section above.	Dilution (response) Grade* 1:1 4, severe 1:2 4, moderate 1:4 1, slight *tissue response severity is graded on a scale of 0-4
Sensitization	Guinea Pig Maximization (Magnussen/Kligman Method) (Saline & cottonseed oil extracts)	Grade I, Weak response; equivalent to negative control
Intracutaneous Reactivity	USP Intracutaneous Reactivity (Saline & cottonseed oil extracts)	Extracts were negative, passed test.
Acute Systemic Toxicity	USP Systemic Toxicity (Saline & cottonseed oil extracts)	Extracts were negative, passed test.
Subacute Toxicity	Fourteen Day Subacute Intravenous Exposure Study (Saline extract)	Non-Toxic at 50 mL/kg/day
Implantation	USP Seven Day Muscle Implant	USP test requirements not met due to acute tissue response. Macroscopic examination revealed no difference between treated and control, however, microscopic examination showed a device-related irritant response.

Test	Description	Results
Implantation	One Year Intramuscular Implant With and Without Tantalum in Rabbits	Tissue responses to Onyx with or without tantalum were greatest at earlier time points (30, 90 days) but then stabilized and were classified as minimal to mild inflammatory responses at one year. Microscopic examination indicates that the material (with or without tantalum) elicits a similar inflammatory response, and that over the course of the study the response gradually lessens in both cases. The test articles were not observed to migrate from the site of implantation.
Genotoxicity	Bacterial Reverse Mutation Assay Conducted with Test Article Extracts (Saline and DMSO extracts)	Extracts were negative, passed test.
Genotoxicity	In Vitro Mammalian Cell Gene Mutation Test Conducted with Test Article Extracts (Saline and DMSO extracts)	Extracts were negative, passed test.
Genotoxicity	Micronucleus Cytogenic Assay in Mice Conducted with Test Article Extracts (Saline and corn oil extracts)	Extracts were negative, passed test.
Carcinogenicity	Carcinogenicity Using the *ras*H2 Transgenic Mouse Model	Not carcinogenic The device tested contained 8% EVOH dissolved in DMSO containing tantalum (30% w/v).

Animal Studies

The objectives of the animal studies were to evaluate the acute and chronic vascular tissue response to Onyx® and DMSO, to determine device effectiveness of Onyx® as an embolic occlusive agent, and to determine device biocompatibility in the subarachnoid space.

Study of DMSO Angiotoxicity in a Swine Model

The purpose of the study was to determine the injection rates and volumes of DMSO that could be safely used for delivery of the embolization agent in humans. Previous experimental investigations had shown that rapid infusion of DMSO could cause severe vascular toxicities, e.g., vasospasm, hemorrhage, angionecrosis and thrombosis. Further evaluation of DMSO associated vascular toxicity indicated that slower infusion rates minimized angiotoxicity. Twenty-six swine were infused and sacrificed at 10 and 28 days. Times of injection were 30, 60 or 90 seconds for 0.5 and 0.8 mL volumes. Saline was used as the control

vehicle injected into the other rete. Vasospasm was monitored via contrast visualized angiography. A five point grading system was used to quantify the severity of vasospasm. The results indicated that a slow and controlled infusion of DMSO (anhydrous) had no severe or permanent vascular effect in the swine model. A dose rate of 0.5 mL/90 sec. (0.33 mL/min.) resulted in low vasospasm scores, low vasospasm duration times and no permanent vascular damage. At fast injections, i.e., above 0.5 mL/min. or greater, gross and microscopic histopathology revealed inflammatory reactions and intimal hyperplasia.

Acute and Chronic Histopathological Changes in a Swine AVM Model

The purpose of the study was to evaluate the safety and effectiveness of the device as an embolization agent in the swine rete mirabile. A total of 20 swine were used in the study: the left rete was embolized with the embolic agent whereas the right rete was embolized with contrast reagent as a control. Animals were sacrificed at 3, 6 and 12 months. Prior to sacrifice an angiographic assessment of the retia was performed. The study indicated that acute and chronic specimens showed total or near total occlusion of the target rete with no evidence of endothelial denudation or arterial wall angionecrosis. The DMSO and Onyx® delivery volumes and injection rates were well tolerated with no reported vasospasm, neurological deterioration, or behavioral modification post-procedure or during chronic maintenance periods. The delivery catheters functioned as anticipated with no occlusion, rupture or adhesion type technical problems reported. Histopathological results documented the presence of intimal hyperplasia, an inflammatory response, foreign body giant cells and focal disruption of elastica without extravasation of the material into the perivascular space at 3 and 6 months. No significant recanalization, hemorrhage or angionecrosis was reported. At 12 months, specimens exhibited a substantial decrease in the chronic inflammatory response seen at 3 and 6 months. A moderate foreign body response was observed in 4/5 specimens, however no angionecrosis or extravasation of embolic material was observed.

Comparative evaluation of tantalum-enhanced Onyx® formulation in surgically created aneurysms

The purpose of the evaluation was to assess the tissue response, and material handling, e.g., visualization, physico-chemical, properties of the tantalum enhanced HD-500 Onyx® formulation in an in vivo aneurysm model. Side-wall aneurysms were created surgically in dogs and were embolized with either the Onyx® HD-500 formulation with the standard amount of tantalum, or with the Enhanced Onyx® HD-500 tantalum formulation. Six animals were embolized with Enhanced Onyx® HD 500 and two aneurysms embolized with standard Onyx® HD 500 as a control. The 4 week angiographic findings showed that the two formulations caused the same degree of embolization, i.e., 96% to 100%. Observations noted of the tantalum-enhanced formulation were: it provided better visual control during embolization of the necks of the aneurysms; there was slightly more, but acceptable, back-pressure noticed during injection; and the run-on effect was longer due to the increased pressure generated to deliver the tantalum-enhanced formulation.

Histopathology comparison of Onyx® to Guglielmi Detachable Coils (GDCs): Embolization of experimental aneurysms

The study series included both swine and canine animal models with experimental aneurysms surgically created on the common carotid arteries using carotid vein graft techniques. A total of 37 aneurysms in 31 animals were evaluated. Post-embolization evaluations included aneurysm occlusion, parent artery patency, procedural complications, and overall system performance. Sixteen animals in a pivotal series were assessed at 3, 6, and 12 months after treatment. Angiographic assessment of aneurysm fill and arterial patency was obtained prior to animal sacrifice. To determine if Onyx elicited a chronic tissue response equivalent to a currently legally marketed embolic device, the investigators compared histological and pathological results of Guglielmi Detachable Coils (GDCs) to Onyx at 3 and 6-month evaluation time points. Aneurysm embolization was performed using a "flow arrest" technique in which a balloon occlusion catheter was placed in the parent artery with the balloon bridging the aneurysm neck thereby effectively isolating the aneurysm from the parent artery flow dynamics. The temporary interruption of blood flow and stasis within the aneurysm sac permitted delivery and precipitation of the Onyx® material from the pre-positioned delivery catheter. Delivery of Onyx® was staged with alternating periods of balloon deflation to re-establish blood flow through the parent vessel. Angiographic assessment of aneurysm occlusion was performed at the completion of the embolization procedure and again immediately prior to animal sacrifice at designated implant periods. Observations were recorded relative to aneurysm fill, neck remnant, protrusion or migration of embolic material, and vasospasm or thrombotic events associated with the treatment. Delivery of Onyx® within the aneurysm sac was controllable and well tolerated by the animals with no significant technical or procedural incidents that would suggest a compromise of safety in a clinical setting. Pre-sacrifice angiography at 3, 6, and 12 months following embolization confirmed parent artery patency and sustained angiographic obliteration of the aneurysm with no incidence of recanalization. Aneurysm histopathology specimens at 3, 6, and 12 month time periods showed complete healing of the aneurysm neck with acceptable tissue response comparable to GDC treated aneurysms with inflammation diminishing to mild focal collections of lymphocytes and giant cells in 12 month chronic specimens. There was no evidence of aneurysm rupture or wall erosion seen in any specimen. Healthy neointimal tissue remodeling with variably mature endothelial cell growth was observed across the aneurysm neck in continuity with the parent artery lumen in all Onyx® treated aneurysms of the pivotal study group.

Biocompatibility for Long Term Neurological Implants

The purpose of the study was to evaluate the effect of Onyx® in direct contact with neurological tissue in the subarachnoid space as might occur during embolization of vascular malformations and/or the rupture of vascular embolizations during treatment with Onyx®. In this experiment, rabbits were given cisterna magna injections of 6% Onyx, 25% Onyx®, saline or autologous blood as controls. Each animal underwent digital subtraction angiography of the

vertebrobasilar system using a microcatheter system. Animal evaluations were conducted at 2, 4, or 90 days via angiography, and gross and microscopic histopathology. There was a minimal to mild focal or multifocal vasculitis in the meninges adjacent to injected Onyx® polymer on sacrifice days 2 and 4 which was characterized by necrosis of the wall of meningeal veins with slight infiltration of the wall by granulocytes. Proteinaceous exudates were observed in Onyx® treated animals on days 2 and 4 and there was an increase in the incidence and severity of subacute inflammation in the meninges of Onyx® treated animals. On day 90, vasculitis and proteinaceous exudates were not observed in the meninges. Degeneration/necrosis was observed in the medulla oblongata and the cerebellum and assumed two distinct patterns. Subarachnoidal distribution consisted of superficial neuropile and neuronal damage characterized by spheroids, neuronal necrosis, and gliosis. Parenchymal distribution was patchy and not associated with the surface and consisted of localized liquefaction necrosis with reactive gliosis. Parenchymal degeneration/necrosis was of comparable incidence and severity in all groups on day 2 and was considered to be due to mechanical trauma. The distribution of changes in the cerebellum and medulla oblongata of Onyx® treated animals as well as the occurrence of similar changes in the saline and blood groups (days 2 and 4 only) strongly suggest that acute pressure against the bone of the skull was involved in the pathogenesis of changes observed in the rabbit and indicate that direct toxicity of the Onyx® was not a factor. Increased intracranial pressure would most likely result from the combined effects of Onyx® material and associated proteinaceous fluid accumulation, and to the fact that Onyx® is not resorbed or redistributed as saline or blood would be.

<u>One-Year Intramuscular Implant Evaluation of Onyx® with and without tantalum</u>
Intramuscular injection sites were examined microscopically and other tissues were examined microscopically to look for the possibility of adverse tissue responses to Onyx® with and without tantalum, and whether the material migrated into the systemic circulation. Thirty rabbits per group received six intramuscular injections of either EVOH (Onyx® polymer) or EVOH-T (with tantalum) and two intramuscular implants of the control article, USP Reference Standard High-Density Polyethylene. The inflammatory response seen in areas of test article administration was frequently minimal (+1) and occasionally mild (+2) in severity. The inflammatory responses were typical of a localized foreign body reaction and were characterized by macrophages and multinucleate giant cells with fewer numbers of lymphocytes and plasma cells. In summary, the observations indicate that the presence of tantalum in the material did not alter the inflammatory response observed to the embolic material. The histophotomicrographs indicate that the material (with or without tantalum) elicits a similar inflammatory response and that over the course of the study i.e., out to 1 year, the response gradually lessens in both cases. The test articles were not observed to migrate from the site of implantation.

X. SUMMARY OF CLINICAL INFORMATION

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 5 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 5. 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 6 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 6. 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.

Additional Clinical Experience

Histopathology Study of Arterio Venous Malformations (AVMs) Embolized with Onyx®:

To assess Onyx® for potential chronic histotoxic effects, 7 brain AVMs (BAVMs) embolized with Onyx® were surgically excised and submitted for evaluation to a board certified histopathologist. The time from treatment with Onyx® to surgical excision ranged from 3 to 19 months. Histopathological findings generally indicated successful embolization of AVM feeders and reduction of AVM size without ischemic or hemorrhagic complications. There were no indications of vascular necrosis, rupture or extravasation of the Onyx® material. Numerous vessels were observed with disruption of the internal elastic lamina, but there did not appear to be any serious adverse effect on the vessel wall. There were frequent indications of small diameter reformed vascular lumens characterized by endothelialization over well organized masses of Onyx® material, but no evidence of actual recanalization. BAVM embolization with Onyx® did not appear to be definitively associated with any morphologic changes that would be expected to produce adverse clinical sequelae.

MRI/CT Evaluation of AVMs treated with Onyx® or n-BCA:

A retrospective, masked review was conducted on Onyx® and n-butylcyanoacrylate (n-BCA) patients to determine if any direct neurotoxicity was detected in the brain post-AVM embolization using current imaging methods. A central reader reviewed pre- and post-embolization MRI or CT scans, from 73 patients. Fifty-four AVM patients were treated with Onyx® and 19 AVM patients were treated with n-BCA. All MRI and CT studies were evaluated for the presence or absence of gliosis, encephalomalacia, edema, leptomeningeal or parenchymal enhancement and hemorrhage. The study indicated that there is no imaging evidence that these embolic devices are associated with cerebral imaging abnormalities.

XI. RISK/PROBABLE BENEFIT ANALYSIS

Wide-neck aneurysms are difficult to treat by surgical clipping or coiling. Aneurysms with wide necks can not often structurally retain embolization coils

and complications such as protrusion of the coil into the parent artery may occur. Parent vessel permanent occlusion may or may not be a feasible alternative dependent upon collateral blood flow and additional factors. The recent availability of neurovascular stents, in conjunction with coiling, through the Humanitarian Device Exemption regulatory provision has provided an additional approach to treating these difficult-to-treat aneurysms. The Onyx® HD-500 System is designed as an alternative treatment for wide neck aneurysms. Similar to coil devices, embolization with Onyx® is intended to exclude the aneurysm sac from intracranial blood pressure while preserving the parent artery circulation. However, the principle of operation differs, in that the Onyx® material is delivered in a liquid phase through a micro catheter positioned within the aneurysm sac. Onyx® precipitates as a soft polymeric embolus. To date, there is only one product available under the HDE provision for the treatment of wide-neck aneurysms. No products have been cleared or approved via premarket notification or premarket approval processes.

The U.S. IDE study and two European clinical studies closely examined the treatment of nearly 200 aneurysms. These studies reflect treatment of aneurysms deemed by the investigators to be best suited for treatment with Onyx®, and where coiling was thought to be potentially ineffective. Both the IDE and CAMEO safety analyses showed that adverse event rates were not significantly different from a group treated with GDC coils. A similar safety profile was observed with Onyx® data from a 100 patient single center study published by Cekirge, et al.

Variable adverse event rates for endovascular treatment of wide neck aneurysms are reported in the medical literature. This variability is related to differences in patient selection criteria, patient outcome measures, follow-up duration, and small sample sizes for coiling studies. However, within the context of the adverse event rates reported in the medical literature, there is no evidence that patients will be exposed to an unreasonable or significant risk of injury from use of the Onyx® HD-500 System as compared to coiling as a means of treatment for wide neck aneurysms.

In terms of the clinical benefit, 75% (30/40) of patients treated with the Onyx HD-500 System in the IDE study, who met HUD criteria, had ≥90% occlusion of their aneurysm without experiencing a major adverse event, as compared to 62.1% (18/29) in the GDC treated group. In the CAMEO study, 68.3% (43/63) of patients treated with Onyx HD-500 System achieved ≥ 90% occlusion of their aneurysms without a major adverse event.

Extensive mechanical testing and biocompatibility evaluation was performed on the Onyx® HD-500 System, as a whole, as well as on the individual components. All tests met the stated acceptance criteria. Preclinical animal model evaluation demonstrated that the Onyx® HD-500 System could be safely deployed and could effectively embolize aneurysms.

Therefore, it is reasonable to conclude that the probable benefit to health from using the Onyx® HD-500 System for 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 outweighs the risk of illness or injury when used in accordance with the instructions for use and when taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

XII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Neurological Devices Advisory Panel since Onyx® was previously reviewed by the advisory panel for embolization of arteriovenous malformations (P030004), and had been found to be safe and effective. The safety considerations of the use of Onyx® as an embolic agent in the treatment of vascular abnormalities have previously been reviewed and therefore it was determined that this application need not be submitted to the advisory panel. Patients with aneurysms of the type identified in this HUD are not easily treated with approved embolization devices, e.g., coils. This device offers physicians a tool for treating aneurysms that may not be appropriate for treatment by conventional methods.

XIII. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, that the Onyx® HD-500 System with not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on April 11, 2007.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the Physician's Labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See Approval Order.

XV. 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.