

FDA Questions for the Circulatory System Devices Panel
April 10, 2003
P020018
Cook, Incorporated
Zenith™ AAA Endovascular Graft

Safety

1. There was a primary safety hypothesis and additional analyses to evaluate the safety of the Zenith Endovascular Graft, as follows:
 - a. The primary evaluation of safety in the clinical study was based upon the incidence of adverse events and factors related to morbidity within 30 days and were assessed as a composite morbidity score that included 31 specific measures in seven categories: cardiovascular, pulmonary, renal, bowel, wound, neurologic and vascular.
 - b. Technical success included a successfully deployed graft, with angiographic patency. Procedural success (30 day) and treatment success (12 month) were evaluated, incorporating patency, type I and III endoleak, aneurysm enlargement (i.e., for treatment success) and serious adverse events or major complications in their definition. Safety was also assessed in terms of the incidence of patient mortality at 30 days and 12 months, with the need for secondary interventions and conversions to open surgical repair, affects on renal function and device integrity evaluated over 12 months.

Please comment on whether the results of the clinical study with the above mentioned safety endpoints provide reasonable assurance of safety in the intended population.

Effectiveness

2. There were two secondary effectiveness hypotheses and additional analyses to evaluate the effectiveness of the Zenith Endovascular Graft, as follows:
 - a. Twelve-month treatment success and clinical utility provided the basis for the effectiveness hypotheses.
 - b. Additional evidence of device effectiveness is available from study evaluation of technical success, procedural success, and shrinkage of aneurysms, and absence of aneurysm rupture and clinically significant

device migration. An evaluation of aneurysm related death also provides evidence of the effectiveness of the endovascular treatment.

Please comment on whether the results of the clinical study, with the above mentioned endpoints provide reasonable assurance of effectiveness in the intended population.

Safety and Effectiveness

3. A unique aspect of this device is the supra-renal fixation. Please comment on whether the results of the clinical study are adequate to provide reasonable assurance of the safety and effectiveness of this specific feature of the Zenith Endovascular Graft.
4. Another unique aspect of this device is that there are 94 modular components (i.e., 30 bodies, 42 legs, 6 body extenders, 9 leg extenders, 4 occluders, 3 converters) that may be used in the treatment of patients. Section 3.4.3 of the Clinical Summary identifies the components used in the US phase II study. Please comment on whether the clinical data provided are adequate to provide reasonable assurance of the safety and effectiveness of the components of the device that fall outside of the size range or configurations (i.e., the converter and occluder components) of those used in the study.

Device Integrity

5. Based on non-clinical engineering bench studies, clinical observations within and outside of the US and analyses performed on explanted devices, there have been a number of mechanical integrity issues identified with the endovascular graft components of the Zenith Endovascular Graft. These issues include the potential for corrosion, barb separation, stent fracture, suture breaks, and graft material wear. The information available regarding each issue and the probability and potential clinical effects of these potential problems are discussed in Appendix D of the Clinical Summary. While these clinical observations may be associated with additional interventions in some patients, there have been no adverse events attributed to any of these issues in the US. There have, however, been cases outside of the US where structural failures (e.g., barb separations) associated with other factors (e.g., neck dilatation) in absence of adequate patient follow-up have lead to serious clinical sequelae (e.g., aneurysm rupture).

Please comment on the significance of these observations. In addition, please comment on the information in the labeling, such as patient selection and follow-up recommendations, needed to reduce the potential for these observations to occur and to minimize associated adverse clinical effects in patients treated with this device.

Labeling

6. One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events. If you recommend approval of the device, please address the following questions regarding product labeling.

- a. The INDICATION FOR USE for this device is as follows:

The Zenith AAA Endovascular Graft with the H&L-B One-Shot? Introduction System and ancillary components is indicated for the endovascular treatment of patients with abdominal aortic, aortoiliac or iliac aneurysms having morphology suitable for endovascular repair, including:

- ?? Adequate iliac/femoral access (?7.5 mm)
- ?? Non-aneurysmal infrarenal neck length of at least 15 mm
- ?? Neck diameter measured outer wall to outer wall of no greater than 28 mm and no less than 18 mm
- ?? Iliac artery distal fixation site greater than 10 mm in length and no greater than 20 mm in diameter (measured outer wall to outer wall)
- ?? One of the following:
 - ?? An abdominal aortic aneurysm with a diameter ?4 cm
 - ?? An iliac aneurysm with diameter ?3.5 cm
 - ?? Aortic, aorto-iliac, or iliac aneurysm with a history of growth ?0.5 cm per year

Please comment on whether the indications for use adequately define the patient population studied and for which the device will be marketed.

- b. The indications for use include treatment of iliac aneurysms, which is unique to this device as compared to the other approved endovascular grafts. Please comment on whether this indication is appropriate.

[Note: As a point of reference, the indications for use of the approved endovascular grafts are attached as Appendix 1 to this document]

- c. Based on the clinical investigation experience, please comment on whether there are any additional warnings, precautions, or

contraindications that you think should be included, either specific to this device or from a generic standpoint for endovascular grafts.

- d. Please provide any additional comments you have on the labeling.

Training

7. Please comment on the adequacy of the proposed physician training plan, as described in the panel package (Section 5 of the Clinical Summary).

Post-Market Study

8. The sponsor is proposing to conduct a post-approval study on the patients enrolled in the pivotal clinical study. Follow-up on patients will be obtained in accordance with the clinical protocol approved under the IDE for this device. Please comment on the acceptability of this plan, as briefly described in the panel package (Section 4.6 of the Clinical Summary).

Appendix 1

Indications for Use for the Other Currently Approved Endovascular Grafts for Treatment of Abdominal Aortic Aneurysms

W.L. Gore & Associates, Inc.

The EXCLUDER Bifurcated Endoprosthesis is intended to exclude the aneurysm from the blood circulation in patients diagnosed with infrarenal abdominal aortic aneurysms (AAA) disease and who have appropriate anatomy as described below:

- adequate iliac/femoral access;
- infrarenal aortic neck treatment diameter range of 19-26 mm and a minimum aortic neck length of 15 mm;
- proximal aortic neck angulation $<60^\circ$; and
- iliac artery treatment diameter range of 8-13.5 mm and iliac distal vessel seal zone length of at least 10 mm.

Guidant

The ANCURE Tube System is indicated for the endovascular treatment of infrarenal abdominal aortic aneurysms (AAA) in patients having:

- adequate iliac/femoral access;
- infrarenal non-aneurysmal neck length of at least 15 mm and a diameter of no greater than 26 mm;
- distal segment neck length of 12 mm and diameter of no greater than 26 mm; and
- morphology suitable for endovascular repair.

The ANCURE Bifurcated System is indicated for the endovascular treatment of infrarenal abdominal aortic or aorto-iliac aneurysms in patients having:

- adequate iliac/femoral access;
- infrarenal non-aneurysmal neck length of at least 15 mm and a diameter of no greater than 26 mm;
- distal segment lengths of at least 20 mm and diameters no greater than 13.4 mm; and
- morphology suitable for endovascular repair.

The ANCURE Aortoiliac System is indicated for the endovascular treatment of infrarenal abdominal aortic or aorto-iliac aneurysms in patients whose anatomy does not allow the use of a tube or bifurcated device and having:

- adequate iliac/femoral access;
- infrarenal non-aneurysmal neck length of at least 15 mm and a diameter of no greater than 26 mm;
- one distal segment length of at least 20 mm and diameters no greater than 13.4 mm; and
- morphology suitable for endovascular repair.

Medtronic

The AneuRx Stent Graft System is indicated for the endovascular treatment of infrarenal abdominal aortic or aorto-iliac aneurysms having:

- adequate iliac/femoral access;
- infrarenal, non-aneurysmal, neck length of greater than 1 cm at the proximal and distal ends of the aneurysm and an inner vessel diameter 10-20% smaller than the labeled device diameter;
- morphology suitable for endovascular repair; and
- one of the following:
 - aneurysm diameter >5 cm;
 - aneurysm diameter of 4-5 cm and which has also increased in size by 0.5 cm in the last 6 months; or
 - aneurysm which is twice the diameter of the normal infrarenal aorta.