Endeavor® Drug-Eluting Coronary Stent

BETTER BY DESIGN

Representing a significant advance in cardiovascular technology and patient care, Medtronic's Endeavor stent is the first and only of a new generation of drug-eluting coronary stents now available in the US.

The Endeavor stent was designed as a synthesis of the best available medical, material, pharmaceutical and manufacturing technology. Consequently, today the Endeavor stent addresses a significant unmet need: offering the efficacy expected from a drug-eluting stent but with the safety profile more commonly associated with bare-metal stents. The Endeavor stent has been long anticipated and now adds a compelling treatment option for patients and doctors when angioplasty is required for coronary artery disease.

FDA approval of the Endeavor stent followed a unanimous FDA expert-panel recommendation in October 2007, during which the quality and quantity of data from the ENDEAVOR clinical program were repeatedly praised. The body of clinical evidence submitted to the FDA for the approval of the Endeavor stent was the largest ever filed for a drug-eluting coronary stent.

WHAT IS A DRUG-ELUTING STENT?

A stent is a tiny mesh cylinder used during angioplasty—a minimally invasive procedure used to open blocked coronary arteries by inflating a tiny balloon in the vessel at the site of the blockage. The stent is crimped tightly around the balloon so that it expands into the walls of the blocked artery as the balloon is inflated. Once the blockage is cleared, the balloon is deflated and removed. The stent, however, remains in place, providing a scaffold to keep the artery open, restoring normal blood flow to the heart.

A simple metal scaffold isn't always enough to prevent arteries from closing up again. This is because of the growth of new tissue inside the vessel as the artery wall heals after the procedure. To limit this new tissue growth and to reduce the likelihood of the artery becoming blocked again, drug-eluting stents were developed. These stents are coated with a drug that diffuses into the artery wall, slowing tissue growth so that the artery remains open.

COMPONENTS OF ENDEAVOR STENT

When the Endeavor stent was designed, safety was an important issue, but Medtronic's engineers could not have predicted the magnitude and implications of the safety discussion taking place today, and the dramatic turn the medical world has taken because of very late stent thrombosis. It is a testament to the vision of those engineers that the extensive ENDEAVOR clinical program has recorded no cases of very late stent thrombosis, highlighting the biocompatibility of the stent and the associated re-creation of a functional endothelium as the artery wall heals following angioplasty with the Endeavor stent.

The Endeavor stent is composed of the following components:

- **Cobalt alloy stent:** The Endeavor alloy is stronger and denser than that used in the previously available drug-eluting stents. Using this advanced alloy enables a robust structural scaffold to be achieved with extremely thin and smooth stent struts. This creates a flexible, deliverable stent with a low profile around the balloon and deployment that conforms easily to the interior shape of the artery.
- **Zotarolimus antiproliferative drug:** The rapid diffusion of zotarolimus from the stent into the artery wall reduces the chance that the artery will re-close by slowing the growth of new tissue in a critical healing phase, as the artery wall recovers following angioplasty.

- **PC polymer coating:** The Endeavor stent is coated with a highly biocompatible polymer known as PC (Phosphorylcholine) Technology. The surface of the PC polymer is designed to mimic the surface of a natural red blood cell, preventing the presence of the stent from causing inflammation or thrombosis. PC has a long history in medical implants, and was the first FDA-approved polymer applied to a coronary stent.
- **MX®2 and OTW delivery systems:** The Endeavor stent is available on both the over-the-wire and the short-wire, Multi-Exchange (MX2) delivery platforms. Medtronic is the only company to utilize the innovative MX2 system, which combines the best features of over-the-wire and rapid-exchange formats on a single-operator platform. MX2 delivery offers short-wire compatibility and over-the-wire deliverability; it also permits the changing of wires without catheter removal.

ENDEAVOR CLINICAL PROGRAM

The US Food and Drug Administration's approval of the Endeavor stent was based on the largest body of scientific evidence ever submitted for the approval of a new drug-eluting stent. The ENDEAVOR clinical program includes a series of studies involving more than 10,000 patients designed to evaluate the safety and effectiveness of the Endeavor stent. These studies include:

- **ENDEAVOR I:** The ENDEAVOR I (E I) trial (n = 100) was designed to evaluate the safety and efficacy of the Endeavor stent for the care of untreated lesions (blockages) in coronary arteries. The trial met all primary endpoints, including a composite of major adverse cardiac events (MACE) with a rate of 2.0%, a binary restenosis (a renarrowing of the arteries) rate of 5.4% and a target lesion revascularization (TLR—a repeat procedure on the affected artery) rate of 2.0% at 12 months.
- **ENDEAVOR II:** The ENDEAVOR II (E II) trial (n = 1197) was designed to evaluate the safety and efficacy of the Endeavor stent compared to Medtronic's Driver® cobalt alloy stent. As an advanced bare-metal stent, the Driver stent represents a benchmark for safety. The study met all endpoints, including a 48% reduction in target vessel failure (TVF—the combination of TVR and MACE) in the Endeavor group compared to the Driver group, and a 61% reduction in TLR at 9 months. At three years, the Endeavor stent was associated with lower absolute rates of cardiac death, heart attack and stent thrombosis compared to the Driver control. A recent pooled analysis drew upon E II data and reported that the Endeavor stent was associated with numerically lower rates of all evaluated safety measures than the Driver stent.
- **ENDEAVOR II Continued Access:** The Endeavor II continued access registry (n = 296) met its primary endpoint, with a 5.4% MACE rate at 30 days, and demonstrated continued efficacy and safety, with no observations of stent thrombosis (the formation blood clots in the arteries) or late stent thrombosis 30 days after stent implant.
- **ENDEAVOR III (E III):** The performance of the Endeavor stent justified a bold head-to-head comparison with Cypher®, a sirolimus-eluting stent marketed by Cordis Corporation. E III (n = 436) evaluated the safety and efficacy of the Endeavor stent compared to Cypher. Primary among the endpoints was in-segment late lumen loss (also known as late loss) at eight months. At the time of study design, late loss was considered a valuable surrogate marker for clinical outcomes. This supposition had proved accurate for previous drug-eluting stents, but E III began to illustrate crucial differences for the Endeavor stent. Despite comprehensively meeting composite and revascularization efficacy endpoints (TLR, TVF and TVR), E III narrowly missed the primary late loss endpoint. However, the

clinical outcomes for which late loss was included as an indicator were ultimately found be comparable to Cypher at two years, dispelling the correlation between late loss and clinical success in ENDEAVOR trials.

- **ENDEAVOR IV (E IV):** A further indicator of confidence in the Endeavor stent, E IV (n = 1548) evaluated the safety and efficacy of Endeavor in a head to head comparison to the TAXUS® paclitaxel-eluting coronary stent from Boston Scientific Corporation. Study endpoints included TVF, MACE and late loss. At nine months, the study met its primary clinical endpoint, with a TVF rate of 6.8% for Endeavor patients compared to 7.4% for TAXUS patients. Unsurprisingly, following learnings from E III, the late loss endpoint was not met. Twelve-month data presented in October 2007 illustrated that the findings were sustained and, as expected in the short term, there were no statistically significant differences between the safety metrics evaluated for the two stents. The 12-month data also showed that no cases of stent thrombosis were reported after six months.
- **ENDEAVOR Five (E-Five):** E-Five (n = 8318) is a prospective international registry providing a real-world performance and safety evaluation of the Endeavor stent in markets where it is already commercially available. The primary endpoint of E-Five is MACE at 12 months. Interim, 12-month results of E-Five on nearly 2000 patients demonstrate further consistency with the preceding clinical trial program. A low rate of MACE (7.0%) was observed, as was a low rate of TLR (3.8%). The consistency in performance and safety was also observed in more complex patients. For E-Five, 34% of the patients had diabetes and 62% had complex lesions. Despite this complexity, the safety profile previously observed is reinforced by these data. Cardiac death was observed at only 2.0%, myocardial infarction at 1.3% and stent thrombosis of only 1.1%. The complete 12-month results on all 8260 patients will be presented at EuroPCR in May 2008.
- **Pooled Safety Analysis:** Specifically requested by the FDA in light of growing safety concerns for first-generation drug-eluting stents, a pooled analysis of safety data from Medtronic's ENDEAVOR clinical program affirmed the superior safety of the Endeavor drug-eluting coronary stent compared to a benchmark for safety, the Driver bare-metal stent. The analysis illustrated that Endeavor (n = 2132), when compared to Driver (n = 596), was associated with low rates of all evaluated safety metrics.

  For the Endeavor stent the respective rates, cumulatively, at three years were:
  –Heart attack (2.7%), stent thrombosis (0.7%), death (3.2%), cardiac death (1.0%).
  For Driver, the rates were:
  –Heart attack (4.2%), stent thrombosis (1.5%), death, (4.5%), cardiac death (2.4%).

  These results mirror those of ENDEAVOR II, a 1200-patient randomized clinical trial that directly compared the Endeavor and Driver stents. In ENDEAVOR II, the Endeavor stent was associated with lower absolute rates of cardiac death, heart attack and stent thrombosis in follow up to three years.