

Section 4

Labeling

The Novacor® Left Ventricular Assist System (LVAS) is an approved device (PMA P980012, September 29, 1998). Proposed changes to the labeling described in P980012 / S004 / A007 are limited to the Indication for Use (Physician's Manual, *Section 3, Indications*), and to the clinical data (Physician's Manual, *Section 7, Clinical Study*).

Section 3, *Indications* and Section 7, *Clinical Study* of the current Physician's Manual are provided in Attachment 4.A. The proposed changes to Section 3 and to Section 7 of the Physician's Manual are provided in Attachment 4.B.

Proposed changes to the *Device Reliability* section of the Physician's Manual (also included in Section 7) have been reviewed by FDA under the auspices of [REDACTED] and are currently being reviewed by FDA via a separate PMA Supplement ([REDACTED]). The proposed change to the reliability labeling of Section 7 is excerpted from [REDACTED] and is provided in Attachment 4.B herein.

APPENDIX

Proposed Labeling

Section 3 of Physician's Manual

Indications for Use (additions in *italics*)

“The LVAS is intended for use as a *short or long-term* bridge to transplantation in cardiac transplant candidates, *and in patients with relative contraindication to transplantation who are expected to become transplant candidates with mechanical circulatory support*, at risk of imminent death from nonreversible left ventricular failure. The LVAS is indicated for use both inside and outside of the hospital.”

Section 7 of Physician's manual

Proposed new material for Section 7 is indicated in red text in the following:

Patients with Relative Contraindications to Transplantation:

Within the clinical study were 75 LVAS recipients and 12 controls subjects who exceeded at least one of the following criteria at study enrollment/device implant. These conditions may be considered relative contraindications to transplant listing

- Serum creatinine > 2.5 mg/dL
- Pulmonary artery systolic pressure > 60 mmHg
- Pulmonary vascular resistance > 6 Wood units (1 Wood unit = 80 dyne-sec/cm⁵)
- Total bilirubin > 5.0 mg/dL
- Body mass index > 32 kg/m² or < 19 kg/m²
- An additional criterion possibly associated with higher transplant risk, age ≥ 66 years, was included due to clinician interest

Forty-nine of 75 LVAS recipients (65%) in the relative-contraindication subgroup were ultimately transplanted. For comparison, 84 of 115 LVAS recipients (70%) without such an identified relative contraindication were transplanted. Only 13 of 35 (37%) Study controls were transplanted. Survival for LVAS recipients with one or more of the relative-contraindications was 50% at one year (by Kaplan-Meier analysis). A majority (8 of 15) of

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recipients supported for a year or longer in the study were from among the 75 recipients with one or more of the relative contraindications

Survival for LVAS recipients with at least one relative contraindication (median survival roughly one year) was highly superior to that of control subjects with similar contraindications (control n=12, median survival 7 days, $p < 0.0001$). Survival of these LVAS recipients was equally superior to that of all control subjects in the Study, regardless of subgroup (control n=35, median survival 11 days, $p < 0.0001$). The recipient supported longest within the relative-contraindication subgroup died without transplant at 34.3 months.

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Preimplant Risk Factors A multivariate risk model derived from the bridge-to-transplant study considers the relative mortality hazard of the five patient factors that were simultaneously significant for mortality in the clinical study (antihypertensive medication at enrollment, body mass index, BUN, history of preimplant cardiac arrest or cardiopulmonary resuscitation, preimplant diabetes) along with three variables commonly of interest (age, gender, etiology) and three variables associated with potential relative contraindications to transplant listing (total bilirubin, serum creatinine, pulmonary artery systolic pressure). Predictions derived from this model closely match survival observations within the study.

**Multivariate Hazard Analysis, all variables significant
following statistical reduction of variables plus six variables of clinical interest (see text)**

Patient Characteristic	No. of subjects with data	% or Mean Value*	Hazard Ratio	p	H.R. 95% LCL	H.R. 95% UCL	Units
LVAS Therapy	225	n/a	0.095	<.0001	0.047	0.194	vs control
On Antihypertensive Medication	225	48%	0.548	0.0272	0.321	0.934	vs none
Body Mass Index	225	26.2	0.947	0.0667	0.893	1.004	/kg/m ²
BUN	223	36.1	1.228	0.0065	1.059	1.423	/10mg/dL
Cardiac Arrest or CPR within previous 48 hours	225	13%	2.878	0.0016	1.490	5.559	vs none
Diabetes	225	21%	1.952	0.0198	1.112	3.425	vs none
Age	225	49	1.093	0.4825	0.852	1.403	/10 years
Gender	225	85% male	1.497	0.1956	0.812	2.759	if female
Etiology	225	48% ischemic	0.729	0.2313	0.434	1.223	if non-ischemic
T. Bilirubin	213	1.66	1.098	0.1854	0.956	1.260	/mg/dL
Serum Creatinine	224	1.6	0.983	0.9351	0.652	1.483	/mg/dL
PA Systolic Pressure	219	48.1	1.061	0.6095	0.846	1.330	/10mmHg

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