SUMMARY OF SAFETY AND PROBABLE BENEFIT

Menssana Research, Inc. Heartsbreath Test for Grade 3 Heart Transplant Rejection

I. General Information

Device Generic Name: Breath test for grade 3 heart transplant rejection

Device Trade Name: Heartsbreath

Applicant's Name and Address:

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Humanitarian Device Exemption (HDE) Number: H030004

Date of Humanitarian Use Device Designation: October 23, 2002

Date(s) of Panel Recommendation: Not applicable (See Section XII for discussion)

Date of Good Manufacturing Practice Inspection: January 22, 1999

Date of Notice of Approval to Applicant: February 24, 2004

II. Indications for Use

The Heartsbreath test is indicated for use as an aid in the diagnosis of grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The Heartsbreath test is intended to be used as an adjunct to, and not as a substitute for, endomyocardial biopsy. The use of the device is limited to patients who have had endomyocardial biopsy within the previous month.

III. Contraindications

There are no known risks to breathing into the Heartsbreath instrument.

IV. Warnings and Precautions

- Every patient should be given a fresh new valved mouthpiece unit before the breath collection apparatus is used, in order to avoid the risk of cross infection between patients.

- Heartsbreath is not a substitute for endomyocardial biopsy – both tests should be used in combination to detect grade 3 heart transplant rejection.

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- The Heartsbreath test result should be compared to biopsy performed within the previous month.

- The Heartsbreath test should not be used for patients who have received a heart transplant more than one year ago.

- The Heartsbreath test should not be used for patients who have grade 4 transplant rejection because Heartsbreath has not been evaluated in these patients.

V.   Device Description

The Heartsbreath test is a non-invasive breath test for markers of oxidative stress which may predict the probability of grade 3 rejection in heart transplant recipients who received their transplants in the preceding year. It consists of:

- A breath collection apparatus for collection of volatile organic compounds in alveolar breath onto a sorbent trap, as well as for the collection of a separate sample of room air.

- Analysis of the volatile organic compounds in alveolar breath and room air by gas chromatography and mass spectroscopy.

- Interpretation of the volatile organic compounds with a proprietary algorithm in order to predict the probability of grade 3 heart transplant rejection.

VI.   Alternative Practices or Procedures

The conventional procedure used in the diagnosis of all grades of heart transplant rejection is endomyocardial biopsy.

VII.   Marketing History

The Heartsbreath test has not been marketed in the United States or any foreign country.

VIII.   Potential Adverse Effects of the Device on Health

- There is a risk of cross infection if a fresh new valved mouthpiece unit is not used in the breath collection apparatus for each patient.

- The Heartsbreath test could yield a false positive or false negative result, and result in inappropriate medical management.

IX.   Summary of Preclinical Studies: None relevant

X.   Summary of Clinical Information

The Heartsbreath test employs a set of breath markers of oxidative stress[1]; it was evaluated in a multicenter clinical study supported by the National Heart Lung and Blood Institute. The study was entitled: Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (the HARDBALL study). [2, 3]

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Background: The original clinical study evaluated a new marker of heart transplant rejection, the breath methylated alkane contour (BMAC). Rejection appears to be accompanied by oxidative stress which degrades membrane polyunsaturated fatty acids, evolving alkanes and methylalkanes which are excreted in the breath as volatile organic compounds (VOCs).

Methods: 1061 breath VOC samples were collected from 539 heart transplant recipients prior to scheduled endomyocardial biopsy. Breath VOCs were analyzed by gas chromatography and mass spectroscopy, and the BMAC was derived from the abundance of C4-C20 alkanes and monomethylalkanes. The gold standard of rejection was the concordant set of International Society for Heart and Lung Transplantation (ISHLT) grades in biopsies read by two cardiac pathologists.

Results of Concordant Biopsies (Two Cardiac Pathologists):

Severity of rejection	ISHLT grade[4]	Number of patients	Percentage of total
None	0	645	60.8%
Mild	1A	197	18.6%
	1B	84	7.9%
Moderate	2	93	8.8%
Severe	3A	42	4.0%

No patients with grade 3B or grade 4 rejection were observed. A combination of 9 VOCs in the BMAC assigned the probability of grade 3 rejection. Comparisons of grade 3 rejection assigned respectively by the site pathologist (usually a general pathologist) readings of the endomyocardial biopsies and the breath test are shown below (TP = true positives, TN = true negatives, FP = false positives, FN = false negatives).

ISHLT Grade of rejection

0, 1 & 2   3

		0, 1 & 2	3
Single site pathologist	0, 1 & 2	TN = 557	FN = 19
assignment	3	FP = 17	TP = 14

		0, 1 & 2	3
Breath test	0, 1 & 2	TN = 600	FN = 17
assignment	3	FP = 419	TP = 25

	Site pathologist	Breath test
Sensitivity	14/33 = 42.4%	25/42 = 59.5%
Specificity	557/574 = 97.0%	600/1019 = 58.8%
Positive predictive value	14/31 = 45.2%	25/444 = 5.6%
Negative predictive value	557/576 = 96.7%	600/617 = 97.2%

Conclusions: A breath test for markers of oxidative stress was more sensitive and less specific for Grade 3 heart transplant rejection than a biopsy reading by a single site pathologist, but the negative predictive values of the two tests were similar. A screening breath test may provide supportive information to help identify heart transplant recipients who are at low risk for grade 3 rejection.

XI. Risk/Probable Benefit Analysis

The direct risk of performing the Heartsbreath test is minimal, because collecting breath is a non-invasive and intrinsically risk-free procedure. The only risk to the patient is cross infection, which can be greatly minimized by replacing the mouthpiece unit before every breath collection. Another risk may arise from the interpretation of the Heartsbreath test because a result may conflict with a biopsy report. This risk is minimized by recommending secondary biopsy review by a second pathologist prior to considering any change in treatment.

These risks must be balanced against the risks of *not* using the Heartsbreath test: a patient might get the wrong treatment because of a false positive or a false negative endomyocardial biopsy report. Biopsy reports can be skewed by two kinds of error. First, there may be a sampling error because rejection tends to be a patchy process, and a biopsy sample may show a lower intensity of rejection than the rest of the heart [5, 6]. Second, the grading of rejection in a heart transplant biopsy is subjective and may therefore be influenced by observer bias. This contention is supported by studies which found high inter-observer variability in scoring the severity of heart transplant rejection. [7-9]

The Heartsbreath test is an objective test that is not skewed by observer bias. The major potential benefit of the Heartsbreath test is that it may reduce the risk of a patient getting the wrong treatment because of an erroneous biopsy report. These benefits are of two kinds: first, the Heartsbreath test may help identify patients with grade 3 rejection and a false negative biopsy report, which may help protect them from undertreatment of a life-threatening condition. Second, the Heartsbreath test may help identify patients with a false positive biopsy report who do not have grade 3 rejection, and may help protect them from the hazards of unnecessary treatment with steroids and other immunosupressant medications.

XII. Panel Recommendation

Pursuant to 21 CFR 814.116(a), this HDE was not referred to the Clinical Chemistry and Clinical Toxicology Devices Panel for review and recommendation because this device is used as an adjunct to endomyocardial biopsy rather than replacing endomyocardial biopsy. Endomyocardial biopsy is the standard of practice to determine heart transplant rejection. No additional safety issues are raised by this indication for use.

XIII. CDRH Decision

CDRH determined that, based on the data submitted in the HDE, the Heartsbreath test for grade 3 heart transplant rejection will not expose heart transplant patients to an unreasonable or significant risk or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval order on February 24, 2004.

XIV. Approval Specifications

Directions for Use: See professional and patient labeling (attached)

Contraindications, Indications for Use: See professional and patient labeling (attached).

Post-approval Requirements and Restrictions: See Approval Order

XV. References

1. Phillips M, Cataneo RN, Greenberg J, Gunawardena R, Naidu A, Rahbari-Oskoui F. Effect of age on the breath methylated alkane contour, a display of apparent new markers of oxidative stress. J Lab Clin Med 2000; 136:243-9.
2. Phillips M, Boehmer J, Cataneo R, et al. Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (the HARDBALL study). J American College of Cardiology 2002; 1:12-13.
3. Phillips M, Boehmer J, Cataneo R, et al. Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (the HARDBALL study). The Journal of Heart and Lung Transplantation (accepted for publication).
4. Billingham ME, Cary NR, Hammond ME, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. The International Society for Heart Transplantation. J Heart Transplant 1990; 9:587-93.
5. Nakhleh RE, Jones J, Goswitz JJ, Anderson EA, Titus J. Correlation of endomyocardial biopsy findings with autopsy findings in human cardiac allografts. J Heart Lung Transplant 1992; 11:479-85.
6. Sharples LD, Cary NR, Large SR, Wallwork J. Error rates with which endomyocardial biopsy specimens are graded for rejection after cardiac transplantation. Am J Cardiol 1992; 70:527-30.
7. Nielsen H, Sorensen FB, Nielsen B, Bagger JP, Thayssen P, Baandrup U. Reproducibility of the acute rejection diagnosis in human cardiac allografts. The Stanford Classification and the International Grading System. J Heart Lung Transplant 1993; 12:239-43.
8. Shanes JG, Ghali J, Billingham ME, et al. Interobserver variability in the pathologic interpretation of endomyocardial biopsy results. Circulation 1987; 75:401-5.
9. Winters GL, McManus BM. Consistencies and controversies in the application of the International Society for Heart and Lung Transplantation working formulation for heart transplant biopsy specimens. Rapamycin Cardiac Rejection Treatment Trial Pathologists. J Heart Lung Transplant 1996; 15:728-35.

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