FEB 26 1998

K973000

510(k) SUMMARY
FOR THE ALIMENTERICS LARA BREATH TEST SYSTEM

I. SYSTEM SPONSOR

A. Sponsor Name and Address

Alimenterics, Inc.
301 American Road
Morris Plains, NJ 07950
(973) 285-3100

B. Official Correspondent and Address

Janet George Murnick, Ph.D.
President and CEO
Alimenterics, Inc.
301 American Road
Morris Plains, NJ 07950
(973) 285-3100

II. SYSTEM IDENTIFICATION

A. Trade/Proprietary Name of the System

The Alimenterics LARA Breath Test System is comprised of two components:

(1) the Pylori-Chek Breath Test Kit; and
(2) the LARA™ (Laser Assisted Ratio Analyzer) System

B. Common Name of the System

^{13}C-Urea breath test for the presence of *Helicobacter pylori*

III. PREDICATE DEVICE

The CLOtest® is a slide with a dispersed gel, which contains urea and a pH indicator. A biopsy acquired during endoscopy is immersed in the CLOtest® gel. If urease activity (associated with *H.pylori*) is present in the specimen, ammonia is generated, causing a pH change. This pH change is detected by the change in color of the pH indicator within 24 hours.

IV. BACKGROUND

Peptic ulcer disease is a chronic inflammatory condition of the stomach and duodenum. Despite the fact that the disease has relatively low mortality, it results in substantial suffering of those affected.

A strong association between *H. pylori*, chronic superficial gastritis and gastrointestinal disease has been well established. *H.pylori* is associated with type B gastritis,[1,2] duodenal ulcer,[3,4] gastric ulcer,[5,6] gastric cancer[7], and non-Hodgkins lymphoma.[7]

H. pylori was first cultured successfully from human gastric mucosa in 1982.[8] The organisms, spiral gram negative bacteria, are found in the human stomach between the gastric epithelium and the mucosa. Isolates implicated in the above mentioned diseased states are distinguished by the production of copious amounts of endogenous urea amidohydrolase (urease).[9,10] The enzyme catalyzes the breakdown of urea to carbon dioxide and ammonia, which are absorbed into the bloodstream.

Several methods are employed to determine the presence of *H. pylori* in the gastointestinal tract. Histologic staining of biopsy tissue using various stains has been shown to give adequate results with a specificity of over 90%.[11] Mucosal biopsy samples can be cultured using selective and non-selective enriched media. However, due to the exacting needs of the organism, culture is the least sensitive (70-80%)[11] of all available techniques. Direct detection of urease activity of biopsy specimens is achieved by placing tissue in Christensen's urea agar and observing a color change. Biopsy and its associated analytic techniques are invasive and not particularly helpful in screening. Non-invasive tests consist of serum assays for IgG and IgA antibodies against *H. pylori*. However, these are not indicative of current infection. Urea breath tests using the radioactive isotope ^{14}C or the stable isotope ^{13}C can detect current infection with *H. pylori*, and have been shown to be highly sensitive methods.[12,13]

V. DEVICE DESCRIPTION

The Alimenterics LARA Breath Test System is based on the ability of the *H.pylori* organism to produce large amounts of the enzyme urease, which hydrolyses urea to NH_4^+ and CO_2, the latter being exhaled. Using ^{13}C-labeled urea, an increase in the ratio of $^{13}CO_2$ to $^{12}CO_2$ over time is an indication for the presence of *H. pylori*. This change can be detected by the LARA System based on a comparison of pre- and post-ingestion measurements of the patient's breath.

The Alimenterics breath test procedure involves a pre-ingestion analysis of a sample of the patient's breath to determine the baseline ratios of $^{13}CO_2$ to $^{12}CO_2$. Following ingestion of a test meal and 100 mg ^{13}C-labeled urea, breath samples are collected at thirty and sixty minutes thereafter. The samples are then introduced into the LARA analyzer which, based on the laser

optogalvanic effect, measures the ratio of $^{13}CO_2$ to $^{12}CO_2$. The results of the three readings, with respect to a calibration standard, are determined concurrently by the analyzer. A specified change in the ratio of $^{13}CO_2$ to $^{12}CO_2$ in the 30 or 60 minute samples as compared to the baseline sample constitutes a positive test. Test values are generated and a report is printed for each patient.

VI. INTENDED USE

The Alimenterics Pylori-Chek Breath Test kit is intended for use with the LARA Breath Test System for the qualitative detection of urease associated with *Helicobacter pylori* as an aid in the diagnosis of *H.pylori* infection.

VII. SUBSTANTIAL EQUIVALENCE COMPARISON

The Alimenterics LARA Breath Test System and the CLOtest® have the same basic intended use: to detect the presence of *H.pylori* in human gastric mucosa.

The same chemical reaction (hydrolysis of urea catalyzed by *H. pylori* urease) forms the basis of both tests. When *H. pylori* is present, urea introduced either by ingestion in the case of the LARA Breath Test System or by contact in the case of the CLOtest, hydrolyses the urease produced by the *H. pylori*, which in turn produces both CO_2 and NH_4. As explained above, with the CLOtest®, this chemical reaction takes place <u>in vitro</u> using an endoscopic biopsy; if *H. pylori* is present, the generation of NH_4 causes a pH change, which is reflected by a change in the color of the pH indicator. With the Alimenterics LARA Breath Test System, the chemical reaction takes place <u>in vivo</u>, and results in an increase in $^{13}CO_2$ in the patient's excreted breath which is detected with the LARA instrument.

A table comparing the technological characteristics of both systems follows:

	Organism	**Reagent**	**Detection of Urea Degradation**	**Physical Safety**	**Time**	**Temp.**
CLOtest®	*H.pylori*	Urea	Visual detection of urea degradation: Urea→NH_4→Color Change	Requires invasive tissue sampling	3-24 hrs.	Requires incubation at 35 or 37° C
Alimenterics Breath Test	*H.pylori*	^{13}C-Urea	LARA detection of excess $^{13}CO_2$: ^{13}C-Urea→$^{13}CO_2$	No tissue sampling; no adverse effects from ingestion of ^{13}C-Urea	1 hr.	LARA operates at ambient temps.

VIII. PERFORMANCE DATA

A. Clinical Tests

Clinical studies were conducted using the LARA Breath Test System. The objectives and results of the Pivotal and Supplemental studies are summarized below:

1. Pivotal Study

The objectives of the study were to evaluate the ability of the LARA Breath Test System to detect the presence of *H. pylori* infections in the gastrointestinal system and to evaluate the sensitivity and specificity of the System as compared to reference methods. One thousand forty eight subjects were enrolled at 10 clinical sites. Of the 1048 subjects, 875 were included in the analysis. All patients who ingested the ^{13}C-urea solution were included in the safety analysis. Only four patients reported adverse events. None of the adverse events was considered to be device related. Based on the results in this study, a diagnostic cutoff of 7.8δ was calculated with an indeterminate zone between 7.01δ and 8.60δ (which excluded 4.1% of the patients).

Data were analyzed using five different reference standards: the IDE protocol standard, the CDER standard, the CDRH standard, the CLOtest, and central histopathology. Overall study sensitivity ranged between 91.29% and 94.15%, specificity ranged from 90.38% to 91.21%, PPV ranged from 90.50% to 91.51%, and NPV ranged from 90.93% to 94.12%. PPVs above 91% and NPVs above 94% were obtained for the breath test using all five reference standards.

During this study, some breath samples did not contain enough CO_2 to permit LARA System analysis. The Pylori-Chek breath collector used a desiccant to remove water vapor from the breath samples. The dessicant was found to absorb both water vapor and CO_2. The device was modified to improve water vapor removal without affecting CO_2 content. A supplemental study, the "cold trap" study was conducted to evaluate the modified device.

2. Supplemental ("Cold Trap") Study

The objectives of the study were to verify that the modified breath test system performed comparably to the device used in the Pivotal Study and to provide an independent test (challenge) of the sensitivity and specificity calculated using the diagnostic cutoff and indeterminate zone determined in the Pivotal Study. Four hundred thirty-two patients were enrolled in this study. Four hundred thirty-one patients attempted to take the Pylori-Chek Breath Test and, of those, 397 were included in the analyses.

Of the 431 patients, six patients reported adverse events. The adverse events were considered to be related to either the endoscopy procedure or to ingestion of the test meal which in some instances followed the procedure by as little as one hour.

Results using the modified device were compared to results obtained in the Pivotal Study using the previous device. In the Pivotal Study, 120 (3.9%) of the breath samples had low CO_2 content, while in this study only 32 (2.5%) of the samples had low CO_2. The device modification reduced the number of UAP samples due to low CO_2 content.

Using the diagnostic cutoff of 7.8δ with an indeterminate zone of 7.01 to 8.60δ (which excluded 3.2% of the patients), sensitivity ranged from 90.09% to 93.21% and specificity ranged from 98.04% to 98.11%, PPV ranged from 98.54% - 98.58%, and NPV ranged from 86.71% to 91.23% using the same five reference standards that were used in the Pivotal Study. These results were comparable to those obtained in the Pivotal Study where sensitivity ranged from 91.29% - 94.15% and sensitivity ranged from 90.38% to 91.21%. The specificity increased by more than 7%. These results of an independent data set using any of the five reference standards show that the high sensitivity and specificity observed in the Pivotal Study could be replicated and even improved.

Based on the results in this study, an ROC analysis was performed to yield a cutoff to maximize total predictive value. Using these results, a cutoff of 6.1δ was calculated with an indeterminate zone between 5.51δ and 6.70δ (which excluded 3% of the patients). Using the 6.1δ cutoff, sensitivity ranged from 92.92% to 96.05%, specificity ranged from 95.97% to 96.71%, PPV ranged from 97.29% to 97.84%, and NPV ranged from 89.24% to 93.59%. The modified device will be used in the clinical product. Thus, results for the diagnostic cutoff, and indeterminate zone determination, obtained with this device should be used for clinical decisions.

B. Nonclinical Tests

In addition to clinical tests, Alimenterics conducted several nonclinical tests that demonstrated the performance of the Alimenterics LARA Breath Test System. These tests included the following:

Storage of Breath Specimens. This study demonstrated that the breath collectors could retain a sufficient amount of CO_2 from a breath sample for 30 days under typical storage conditions. The study established a 30 day shelf life.

Transport Study. This study demonstrated that the breath collectors could retain a sufficient amount of CO_2 from a gas sample after experiencing the extreme transport condition.

Control Stability. The first control stability study did not demonstrate that the breath collectors could retain a sufficient amount of CO_2 from a control sample for 60 days under

varied storage conditions. Because a control failure occurred during the first study, a second study is being conducted to demonstrate that breath collectors packaged in sealed pouches currently used in the final product could retain a sufficient amount of CO_2 from a control sample for 60 days under varied storage conditions including hot, humid conditions and cold, low pressure conditions.

Carryover Study. The data showed that the batch carryover effect ranged from 0.67% to 2.13%, with an average of 1.67% and a standard deviation of .51%. This study demonstrated that samples with high ^{13}C content do not affect the baseline result of the next patient specimen.

Verification of Calibration (Control Frequency) Study The study demonstrated that the LARA System can maintain calibration for an 8 hour period using one control sample.

Intersystem Comparison. The study demonstrated that analysis of a control gas was reproducible using three different LARA Systems.

C. Conclusions

The clinical studies demonstrate that the Alimenterics LARA Breath Test System performs comparably to other diagnostic methods for the presence of *H.pylori* in the human gastrointestinal tract, including the CLOtest®. In the clinical studies of the Alimenterics LARA Breath Test System, there were no adverse events directly associated with the system. The breath test system is, thus, safer than those test methods, like the CLOtest®, that require a biopsy for evaluation. The nonclinical studies demonstrate that the Alimenterics LARA Breath Test System performs reliably under the anticipated conditions of usage.

IX. BIBLIOGRAPHY

1. Andersen LP, Holck S, Poulsen CO, Elsborg L, Justesen T. *Campylobacter pyloridis* in peptic ulcer disease. Scand. J. Gastoenterol. 22: 219-224, 1987.

2. Blaser MJ. Gastric *Campylobacter*-like organisms, gastritis and peptic ulcer disease. Gastroenterol. 93: 971-83, 1987.

3. Langenberg ML, Tytgat GNJ, Schipper MEI, Rietra PJGM, Zanen HC. *Campylobacter*-like organisms in the stomach of patients and healthy individuals. Lancet i: 1348, 1984.

4. Marshall, B.J., Guerrant, R.L., Plankey, M.W., et al. Comparison of ^{14}C-urea breath test, microbiology and histology for the diagnosis of *Campylobacter pylori* (Abstract). Gastroenterol. 94:A284, 1988.

5. Graham DY, Klein PD, Opekun AR, Boutton TW. Effect of age on the frequency of active *Campylobacter pylori* infection diagnosed by the [^{13}C]urea breath test in normal subjects and patients with peptic ulcer disease. J. Infect. Dis. 157: 777-780, 1988.

6. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1: 1311-15, 1984.

7. Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, Orentreich N, Vogelman JH, Friedman GD. *Helicobacter pylori* infection and gastric lymphoma. The New England Journal of Medicine 330: 1267-1271, May 1994.

8. Marshall BJ, Royce H, Annear DI, Goodwin CS, Pearman JW, Armstrong JA. Original isolation of *Campylobacter pyloridis* from human gastric mucosa. Microbios. Lett. 25: 83-88, 1983.

9. Hazell SL, Borody TJ, Gal A, Lee A. *Campylobacter pyloridis* gastritis I: detection of urease as a marker of bacterial colonization. Am. J. Gastroenterol. 82: 292-296, 1987.

10. Marshall BJ, Warren JR, Francis GJ, *et al.* Rapid urease test in the management of *Campylobacter pyloridis*-associated gastritis. Am. J. Gastroenterol. 82: 200-10, 1987.

11. *Helicobacter pylori* in peptic ulcer disease. Consensus Development Conference Statement, National Institutes of Health: Feb. 7-9, 1994.

12. Rauws EAJ, Royen EAV, Langenberg W, Woensel JV, Vrij AA, Tytgat GNJ. ^{14}C-urea breath test in *C. pylori* gastritis. Gut 30: 798-803, 1989.

13. Eggers RH, Kulp A, Ludtke FE, Bauer FE. Characterization of the [^{13}C]urea breath test for the diagnosis of *Campylobacter pylori* infections. Stable Isotopes in Paedetriac Nutritional and Metabolic Research: 295-301, 1990.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Janet G. Murnick, Ph.D.
Alimenterics Inc.
301 American Road
Morris Plains, NJ, 07950

FEB 26 1998

Re: K973000
Device: Alimenterics LARA™ Breath Test System
Regulatory Class: I
Product Code: MSQ (LYR)
Dated: August 6, 1997
Received: August 12, 1997

Dear Dr. Murnick:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent for the indications for use stated in the enclosure to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments. You may, therefore, market the device, subject to the general controls provisions of the Federal Food, Drug, and Cosmetic Act (Act). The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, and labeling, and prohibitions against misbranding and adulteration.

In addition, we have determined that your product contains the following component subject to regulation as drugs: ^{13}C-Urea (powder-100 mg).

Our substantially equivalent determination does not apply to the drug component (NDA 20-900) of your product. For information on applicable Agency requirements regarding the drug component, we suggest you contact:

Mark Goldberger, M.D., M.P.H.
Division Director
Division of Special Pathogens
and Immunologic Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 827-2335

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval) it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality Systems Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, FDA will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, the Food and Drug Administration (FDA) may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under section 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification only after the Center for Drug Evaluation and Research has approved the drug component of your product. An FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and permits your device to proceed to the market, but it does not mean that FDA approves your device. Therefore, you may not promote or in any way represent your device or its labeling as being approved by FDA. If you desire specific advice for your device on the labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), promotion, or advertising, please contact the Office of Compliance, Promotion and Advertising Policy Staff (HFZ-302) at (301) 594-4639. Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or (301) 443-6597, or at its internet address "http://www.fda.gov/cdrh/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known): K973000

Device Name: Alimenterics LARA™ Breath Test System

Indications For Use:

The Pylori-Chek Test System is intended for use with the LARA Laser Assisted Ratio Analyzer for the qualitative detection of urease associated with Helicobacter pylori infection in the human stomach and as an aid in the diagnosis of H. pylori infection in symptomatic adult patients. The Pylori-Chek Test system consists of a Pylori-Chek test kit for the collection of breath samples and a LARA Laser Assisted Ratio Analyzer for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in the breath sample.

For use by healthcare professionals. To be administered under a physician's supervision.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K973000

Prescription Use ✓ Or Over-The-Counter Use ____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)