N21-314_ORIG_APPROVAL_PKG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 21-314

Trade Name: IDkit:Hp

Generic Name(s): (containing C-Urea and Citrica)

Sponsor: Oridion BreathID, Inc.

Agent:

Approval Date: December 17, 2002

Indication: Provides for use in kit containing C-Urea (tablet for oral solution), 75 mg and Citrica (citric acid powder for oral solution) 4.0g as an aid for initial diagnosis and post-treatment monitoring of H. pylori infection

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APPLICATION NUMBER:

21-314

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-314

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-314

Oridion BreathID Inc.
ATTN: Daniel Katzman, VP Business Development
21 Highland Circle
Needham, MA 02494-3038

Dear Mr. Katzman:

Please refer to your new drug application (NDA) dated February 2, 2001, received February 2, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IDkit:Hp™ containing ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0 g for the Oridion BreathID® Breath Test System.

We acknowledge receipt of your submissions dated:

July 5, 2000	November 20, 2001	May 7, 2002	November 21, 2002
July 31, 2000	December 4, 2001	May 27, 2002	November 27, 2002
September 7, 2000	December 6, 2001	September 3, 2002	December 4, 2002
November 28, 2000	December 16, 2001	September 18, 2002	December 15, 2002 (2)
January 30, 2001 (2)	January 3, 2002	October 1, 2002 (3)	December 17, 2002
September 3, 2001	January 6, 2002	November 3, 2002	
October 21, 2001	February 4, 2002 (2)	November 14, 2002	
October 26, 2001	February 28, 2002	November 17, 2002	

The June 26, 2002, submission constituted a complete response to our November 30, 2001, action letter.

This new drug application provides for the use of IDkit:Hp™ containing ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0 g for the Oridion BreathID® Breath Test System for use as an aid for initial diagnosis and post-treatment monitoring of *H. pylori* infection.

We have completed our review of this application, as amended and found that it is safe and effective for use as an aid for initial diagnosis and post-treatment monitoring of *H. pylori* infection. Therefore, it is approved, effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted December 15, 2002, carton, and container labels submitted on December 17, 2002). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten

of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-314**." Approval of this submission by FDA is not required before the labeling is used.

The text in italics below addresses the application of FDA's Pediatric Rule at 21 CFR 314.55 to this NDA. The Pediatric Rule has been challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. The government has not yet decided whether to seek a stay of the court's order. In addition, the government has not yet decided whether to appeal the decision; an appeal must be filed within 60 days. **Therefore, this letter contains a description of the pediatric studies that would be required under the Pediatric Rule, if the Pediatric Rule remained in effect and/or were upheld on appeal.** Please be aware that whether or not these pediatric studies will be required will depend upon the resolution of the litigation. FDA will notify you as soon as possible as to whether this application will be subject to the requirements of the Pediatric Rule as described below. In any event, we hope you will decide to conduct these pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on information submitted, we conclude the following:

For use as an aid for initial diagnosis and post-treatment monitoring of H. pylori infection,

- *We are waiving the pediatric study requirement for this application for patients 0-2 years of age.*
- *We are deferring submission of pediatric studies for patients >2-16 years of age until December 31, 2007.*

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to a NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Peacock, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/s/

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure (labeling)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht .
12/17/02 04:45:55 PM
NDA 21-314

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-314

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-314

Oridion Medical 1987 Ltd.
Attention: Richard Eagling
Oridion Medical Inc.
77 Franklin St.
Boston, MA 02110

Dear Dr. Eagling:

Please refer to your new drug application (NDA) dated February 2, 2001, received February 2, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IDkit:H.p. (contains 75 mg of ^{13}C-Urea tablet and Citrica) for the BreathID™ System. The device part of this BreathID™ System was cleared under 510(k) application (K011668) by the Division of Clinical Laboratory Devices in the Office of Device Evaluation, Center for Devices and Radiological Health on July 9, 2001.

We acknowledge receipt of your submissions dated:

May 30, 2001	July 8, 2001	October 10, 2001	October 24, 2001
November 6, 2001	November 12, 2001	November 14, 2001	

We have completed the review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

1. Demonstrate that the FD&C Yellow No. 6 used in this component conforms in identity and specification to the requirements of 21 CFR 74.706(a)(1) and (b). Document that the FD&C Yellow No. 6 is certified in accordance with 21 CFR 80. The documentation from [ ] does not assure compliance with these regulations. Obtain documentation that the dye conforms to 21 CFR 74.706(a)(1) and (b), and has been certified in accordance with 21 CFR 80. Alternatively, certified FD&C Yellow No. 6 may be obtained from a different supplier or the product may be reformulated without the dye.

2. Provide documentation that will allow verification of the suitability of the components of [ ]. For example, a list of individual components and their regulatory references could be obtained from the supplier and submitted to your NDA. Alternatively, the supplier may submit this information in a Drug Master File. The product can also be reformulated without this flavor.

3. Revise the specification for Citrica. Please add a specific identity test for citric acid. In addition, the acceptance criteria for [ ] should be revised. Neither the proposed — limit for [ ] nor the proposed — limit for [ ] is supported by the available stability data. Please tighten the acceptance criteria accordingly or provide further justification for their retention.

4. Explain the cause of the observed failures of the submitted stability samples at both stability storage conditions. Address, for example, issues such as the variability of the data, and pouch integrity. Explain the following finding for batch 235.3 stored at 25°C/60% RH: [ ]

5. Provide new stability data from 3 batches justifying the proposed labeled storage condition of 15-30°C, given the multiple stability failures at both storage conditions. For example, in batch 235.1 at 30°C/60% RH ([ ] months) the following were observed:

   - [
   -
   -
   -]

   If the stability of the product cannot be demonstrated to support the labeled storage condition, propose a markedly reduced expiration dating period or, if appropriate, a different packaging system.

6. Provide additional dissolution data to allow a more therapeutically relevant dissolution specification to be set. We request data from three tablet batches in water using sampling time points of 5, 10, 15, and 30 minutes.

In addition, it will be necessary for you to submit draft labeling revised as suggested in the draft labeling attached and incorporating any changes relating to the deficiencies listed above. If additional information relating to this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application, along with final labeling, is approved.

If you have any questions, call Yoon Kong, Pharm.D, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Division Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rigoberto Roca

11/30/01 05:40:18 PM

Rigoberto Roca, M.D. for Renata Albrecht, M.D.

112 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-314

Approved Labeling

3. Package Insert 005569 L

Package Insert

BreathID® IDkit: Hp™ containing ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0 g for the Oridion BreathID® Breath Test System

Oridion

005569 L

All reference to Oridion in this manual refers to Oridion Medical 1987 Ltd.

The following are trademarks of Oridion Medical 1987 Ltd.; The Oridion® name, Oridion, MCS™, IDcircuit™, , IDcheck™, BreathID®. IDkit: Hp™

Note: No license, expressed or implied, is granted under any of Oridion's patents.

I. Intended Use

The Oridion BreathID® Breath Test System is intended for use in the qualitative detection of urease associated with *Helicobacter pylori (H. pylori)* in the human stomach and as an aid in the initial diagnosis and post treatment monitoring of *H. pylori* infection in adult patients. This test may be used at least four weeks following completion of *H. pylori* eradication therapy. For these purposes, the system utilizes Molecular Correlation Spectrometry (MCS™) for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples.

The Oridion BreathID® Breath Test System consists of the IDkit: Hp™ containing ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0g for the Oridion BreathID® Breath Test System test kit, the BreathID® device and the IDcheck™ system quality control function accessory.

The device is for use by trained healthcare professionals and is to be administered under a physician's supervision.

II. Summary and Explanation

Since the initial identification of *H. pylori* in the early 1980's[1], the management of upper gastrointestinal disease has changed dramatically. "*Helicobacter pylori* is now recognized as an important pathogen and a casual relationship between *H. pylori* and chronic active gastritis, duodenal ulcer, and gastric ulcer is well documented"[2]. Currently there are numerous *H. pylori* detection technologies for upper gastrointestinal disease including biopsy and serum analysis. These technologies depend on two general methods for obtaining a sample for testing; invasive and non-invasive.

Invasive test methods first require an endoscopic gastric biopsy. The tissue collected from the biopsy is examined in a laboratory by microbiological culture of the organism, direct detection of urease activity in the tissue (for example, the CLOtest®), or by histological examination of stained tissue. Biopsy based methods present an element of patient risk and discomfort, and may provide false negative results due to sampling errors.

Serological tests, also invasive, require a blood sample, which is then used to detect serum antibodies to *H. pylori*. These tests suffer the disadvantage of being unable to distinguish between positive active infections and past exposure to infection, and therefore cannot be a conclusive indicator of current *H. pylori* infection.

^{13}C-urea breath tests are a non-invasive, non-radiological, and non-hazardous, analysis of the exhaled breath. The BreathID® test (described in the next section) measures the $^{12}CO_2$ and $^{13}CO_2$ components of the exhaled breath before oral ingestion of ^{13}C-enriched urea to determine the baseline ratio of $^{13}CO_2/^{12}CO_2$. After the patient ingests the ^{13}C-enriched urea, another measurement is obtained to determine the Delta Over Baseline[1] change in the $^{13}CO_2/^{12}CO_2$ ratio.

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[1] Delta Over Baseline is defined as: { ($^{13}CO_2^{(n)}/^{12}CO_2^{(n)} - ^{13}CO_2^{(0)}/^{12}CO_2^{(0)}$)*1000‰}/ ($^{13}CO_2^{(PDB)}/^{12}CO_2^{(PDB)}$)

Wherein PDB is the standard $^{13}C/^{12}C$ isotope ratio (=1.1273%). (0) is the base line measurement and (n) is the measurement of interest.

III. Principles of the Oridion BreathID® Breath Test

The Oridion BreathID® non-invasive breath test is an in-vitro and in-vivo non-radioactive diagnostic test that analyzes a breath sample before and after ingestion of ^{13}C-enriched urea to identify those patients with *H. pylori* infection.

The in-vivo portion of the test begins with the collection of a baseline breath sample. The patient breathes normally while the BreathID® device collects samples through the IDcircuit™ nasal cannula. The IDcircuit™ extracts moisture and patient secretions from the breath samples to provide an accurate CO_2 reading. The patient then ingests a test meal (consisting of 75 mg of ^{13}C-urea and 4 grams of citric acid) and the in-vitro portion of the test begins.

The BreathID® device continually and non-invasively samples the patient's breath and measures the changes in the $^{13}CO_2/^{12}CO_2$ ratio versus the original baseline sample. These changes are displayed as a graph on the large display screen while the in-vivo portion of the test continues. The graph shows multiple points that allow the physician to monitor the patient's dynamic physiological response to the administered urea. Once the BreathID® device has collected enough data to determine whether a patient is positive or negative for *H. pylori*, it automatically ends the test and prints out the results.

Description of the ^{13}C-urea Diagnostic Drug Component

The diagnostic drug component of the kit is ^{13}C-enriched urea prepared as a tablet. The tablet is to be to be dissolved with Citrica powder in a glass of water to provide a clear, colorless solution for oral administration.

The 75 mg ^{13}C-urea drug component is supplied as a tablet in a sealed pouch. The Citrica powder (citric acid [3,4,5], aspartame and Tutti Frutti Flavor) is supplied in a separate sealed pouch.

An average adult body normally contains about 9.0 grams of urea, which is a product of protein metabolism. Urea in the body is referred to as a natural isotopic abundance urea since it is composed of 98.9% ^{12}C-urea and 1.1% ^{13}C-urea.

Greater than or equal to 99% of the carbon molecules in the drug component are in the form of ^{13}C; a stable, naturally occurring, non-radioactive isotope of carbon. ^{13}C-urea is the diamide of ^{13}C carbonic acid and is highly soluble in water (1 gram per ml at 25^{O}C). It has the following chemical formula $^{13}CH_4N_2O$.

Principles of the Test

The Oridion BreathID® breath test requires 75 mg of ^{13}C-urea and 4.3 g Citrica powder to be dissolved in water and then be ingested by the patient. In the presence of urease associated with gastric *H. pylori*, ^{13}C-urea is decomposed to $^{13}CO_2$ and NH_3 according to the following equation:

$$2\ ^{13}\text{C-Urea} + 2\ H_2O \xrightarrow{\textit{H. pylori}\ \text{urease}} 2\ ^{13}CO_2 + 2\ NH_3$$

The $^{13}CO_2$ is absorbed into the blood and then exhaled in the breath. Absorption and distribution of $^{13}CO_2$ is considerably faster than the urease reaction. Therefore, the rate limiting step of the entry process is the cleavage of urea by the urease from *Helicobacter pylori*. In the exhaled breath of *H. pylori* positive patients, the ratio $^{13}CO_2$ to $^{12}CO_2$ increases early after oral administration of ^{13}C-urea.

In the case of *H. pylori*-negative patients, the ^{13}C-urea does not produce $^{13}CO_2$ in the stomach.

IV. Warnings and Precautions

1. For in vitro diagnostic use only. The ^{13}C-urea drug solution is taken orally as part of the diagnostic procedure.
2. Phenylketonurics: Contains Phenylalanine, 84 mg per dosage unit of Citrica powder. For reference, 12 ounces of typical diet cola soft drink contains approximately 80 mg of phenylalanine.
3. In the case of accidental overdose - immediately call your local toxicology center.
4. A negative result does not rule out the possibility of *Helicobacter pylori* infection. False negative results can occur with this procedure. If clinical signs suggest *H. pylori* infection, retest with a new sample or an alternate method.
5. A false positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmanni*.
6. A false positive test could occur in patients who have achlorhydria
7. Antimicrobials, proton pump inhibitors, and bismuth preparations are known to suppress *H. pylori*. Ingesting these medications within two weeks prior to performing the breath test may produce false negative test results.
8. Tiny particles may remain visible in the reconstituted ^{13}C-urea and Citrica solution after thorough mixing for 5 minutes. However, if more substantial particulate matter is still present, the solution should not be used.

V. Shelf Life and Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

The following components of the test kit have expiration dates: ^{13}C-urea tablet and Citrica powder. Do not use either of these components beyond the expiration date stated on the respective labels.

VI. Patient Preparation

Remind the patient that the Citrica contains 84 mg of phenylalanine per packet of Citrica. Phenylketonurics restrict dietary phenylalanine.

The patient should have fasted at least 1 hour before administering the test.

The patient should not have taken antimicrobials, proton pump inhibitors or bismuth preparations within two weeks prior to administering the test.

VII. Procedure

Materials

Materials Provided

Each single-patient Oridion IDkit: Hp™ containing ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0g for the Oridion BreathID® Breath Test System breath test contains:

One IDcircuit™ nasal cannula

One tablet ^{13}C-enriched urea 75 mg

One packet of Citrica powder 4.3 g (4.0 g citric acid, aspartame, Tutti Frutti Flavoring)

One drinking straw

IDcheck™

One IDcheck™ accessory is supplied for each 25 IDkit: Hp™ containing ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0 g for the Oridion BreathID® Breath Test System breath test kits.

The IDcheck™ accessory supplied with the BreathID® kit provides quality control for the BreathID® system.

Materials Needed But Not Provided:

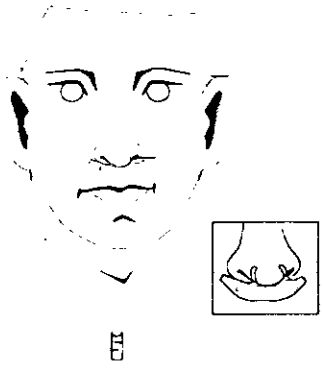
1) A drinking cup with capacity of 8 ounces or greater

2) Tap water

Step by Step Procedure

For detailed information regarding the step by step procedure, on screen instructions, and device operation, refer to the BreathID® Operator's Manual.

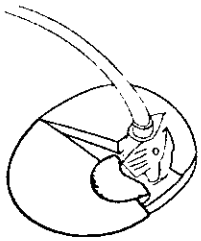
1. Connecting the IDcircuit™



Take the IDcircuit™ out of the plastic bag and slide the tubing sleeve down as far as it will go. Gently place the cannula tips into the patient's nostrils, with the lip guard resting above the upper lip. Place the cannula tubing over the ears.

Slide the tubing sleeve up toward the neck to fit comfortably under the chin.

Connect the IDcircuit™ to BreathID® device by twisting the yellow connector clockwise securely into the BreathID® device.



Verify that the IDcircuit™ is not twisted or kinked, and that the cannula tips are in the nostrils.

2. Preparing the test drink

Note: Administer the test drink within two hours of preparation to maintain solution stability.

Dissolve the Citrica and the ^{13}C-enriched urea tablet in a single drinking cup (6.5 oz / 200ml) of tap water.

Stir thoroughly with a straw for 1 to 2 minutes to be sure that the Citrica powder and the urea tablet are completely dissolved.

Note: Tiny particles may remain visible after thorough mixing. However, if more substantial particulate matter is still present after 5 minutes, then discard the solution and repeat the procedure with a new tablet and powder pack.

3. Administering the test drink and starting measurement

Note: Do not administer the drink until prompted by the device screen instructions.

Ensure that the patient drinks the solution through the straw.

The patient must drink the solution within two minutes and consume the entire amount.

After the patient finishes drinking the solution, press the OK button to proceed.

4. Measurement

The BreathID® device continually analyzes the trend of measured results. When the BreathID® device determines that the final value will be positive or negative, or greater or less than 5 Delta Over Baseline it will automatically end the test and print out the results.

5. Removing and discarding the IDcircuit™

When the measurement is complete, disconnect the IDcircuit™ from both the patient and the device. Dispose of the IDcircuit™ and kit contents according to standard operating procedures or local regulations for the disposal of contaminated medical waste.

Note: If you do not disconnect the IDcircuit™, instructions will appear on the device screen reminding you to do so. The device will not proceed to the next screen until the IDcircuit™ is disconnected.

6. Printing Results

   a. After the measurement is complete, the device will automatically print the test results. The printout contains the graph as seen on the screen including the date, time, Delta Over Baseline value and test number of the last point measured.

   b. Tear off the printed results and fill in the patient data.

VII. Quality Control

The BreathID® device is an in vivo instrument for measuring the ratio of $^{13}CO_2$ to $^{12}CO_2$ in the patient's exhalation. Since the BreathID® is not a laboratory device; no field laboratory quality control procedures are required. The BreathID® device undergoes rigorous quality assurance procedures before leaving the manufacturer.

To ensure correct functioning of the BreathID® in the field, an accessory labeled IDcheck™ is provided with every 25 IDkit: Hp™ containing ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0 g for the Oridion BreathID® Breath Test System. The BreathID® will automatically display a request to perform an IDcheck™ after 25 tests are completed. The BreathID® device will not continue to function unless the IDcheck™ accessory is used as directed.

The IDcheck™ accessory supplied with every 25 IDkit: Hp™ containing ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0 g for the Oridion BreathID® Breath Test System provides quality control for the BreathID® device. Quality control is accomplished by introducing a single-use cartridge that contains a known concentration of CO_2 into the device every 25 breath tests. This procedure confirms that the BreathID® System is functional and is performing within specifications.

VIII. Calibration

The calibration stability of the BreathID® system is ensured by the Oridion proprietary $^{12}CO_2$ and $^{13}CO_2$ Isotope Specific Infrared (ISIR) lamp. The physical process underlying gas discharge emissions supports this stability. The emissions are caused by molecular rotation-vibration transitions, each generating a spectral line at a specific wavelength, uniquely defined to an accuracy of better than 0.01 Å (Angstrom).

Calibration of the BreathID® device is performed automatically if required. Five gas samples of known concentration and isotope ratio are used to adjust the absorption cell calibration curves aiming to attain identical isotope ratios over the collection range of CO_2 concentrations. These gas samples are generated as part of the BreathID® device's normal operation, ensuring accurate readings in both negative and positive samples.

In addition, quality checks are performed by the BreathID® device during every test to ensure the BreathID® System performs within established limits. Refer to the BreathID® Operator's Manual for a complete description of the IDcheck™ procedure.

IX. Test Results

The Test Method

The ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples is determined by Molecular Correlation Spectrometry (MCS™), which is utilized by the BreathID® device software.

Calculation of Results

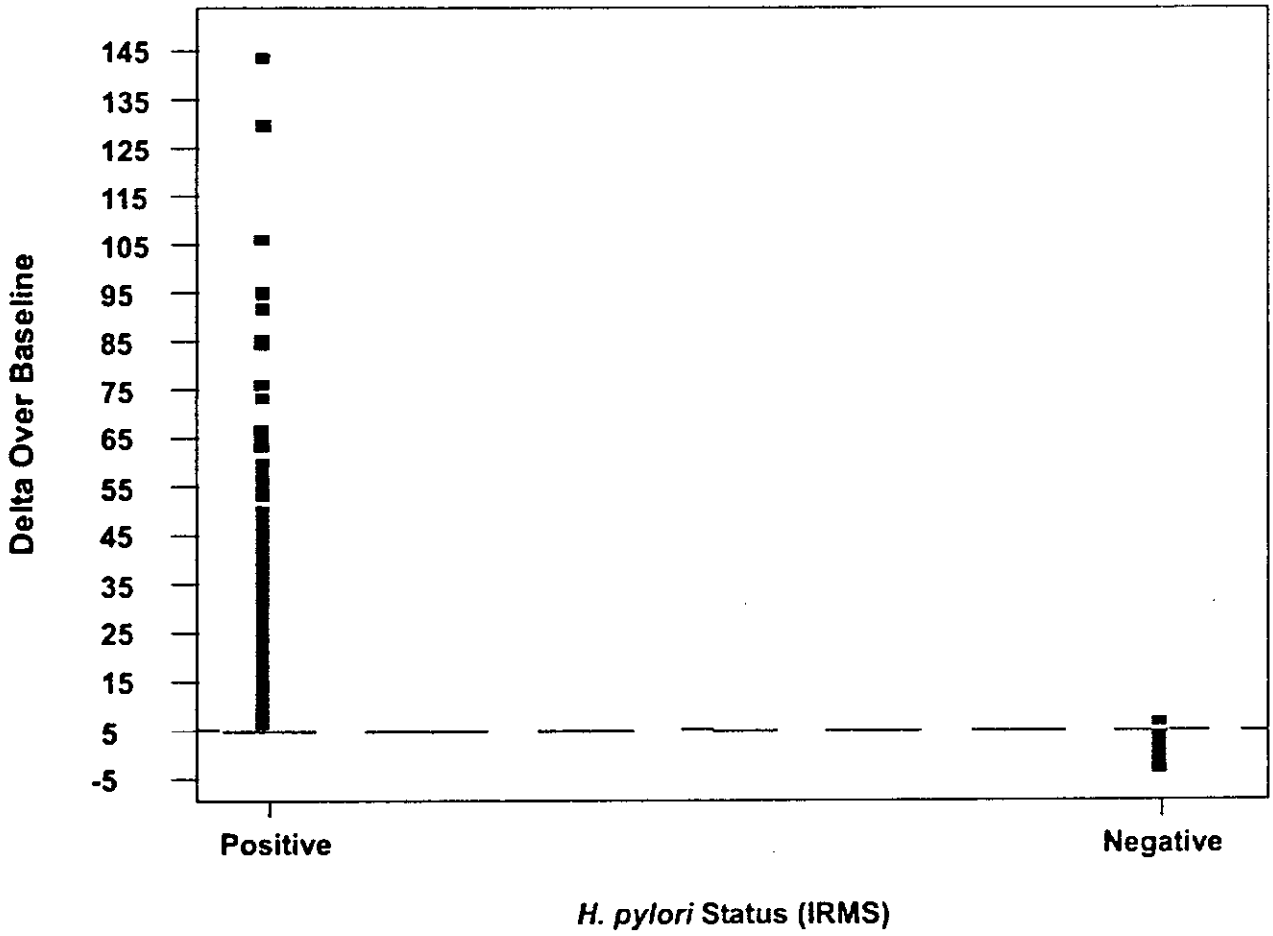
The results of the BreathID® test are provided as the Delta Over Baseline. Delta Over Baseline is the difference between the ratio ($^{13}CO_2/^{12}CO_2$) in the test specimen and the corresponding ratio in the baseline sample. There are no calculations required by the user.

Determination of the Cutoff Point

The cutoff point is the level (threshold) used to discriminate between *H. pylori* infected and non-infected individuals.

The Delta Over Baseline cutoff point was determined to be 5 in a controlled study of 186 adult asymptomatic and symptomatic patients (101 infected and 85 uninfected) in Israel using a local reference standard called the Isotope Ratio Mass Spectrometer (IRMS). The cutoff point was evaluated by determining the BreathID® test result threshold at which positive and negative patients, as determined by the Isotope Ratio Mass Spectrometer, were best distinguished. Figure 1 shows graphically the BreathID® cutoff point, which distinguishes *H. pylori* positive and negative patients.

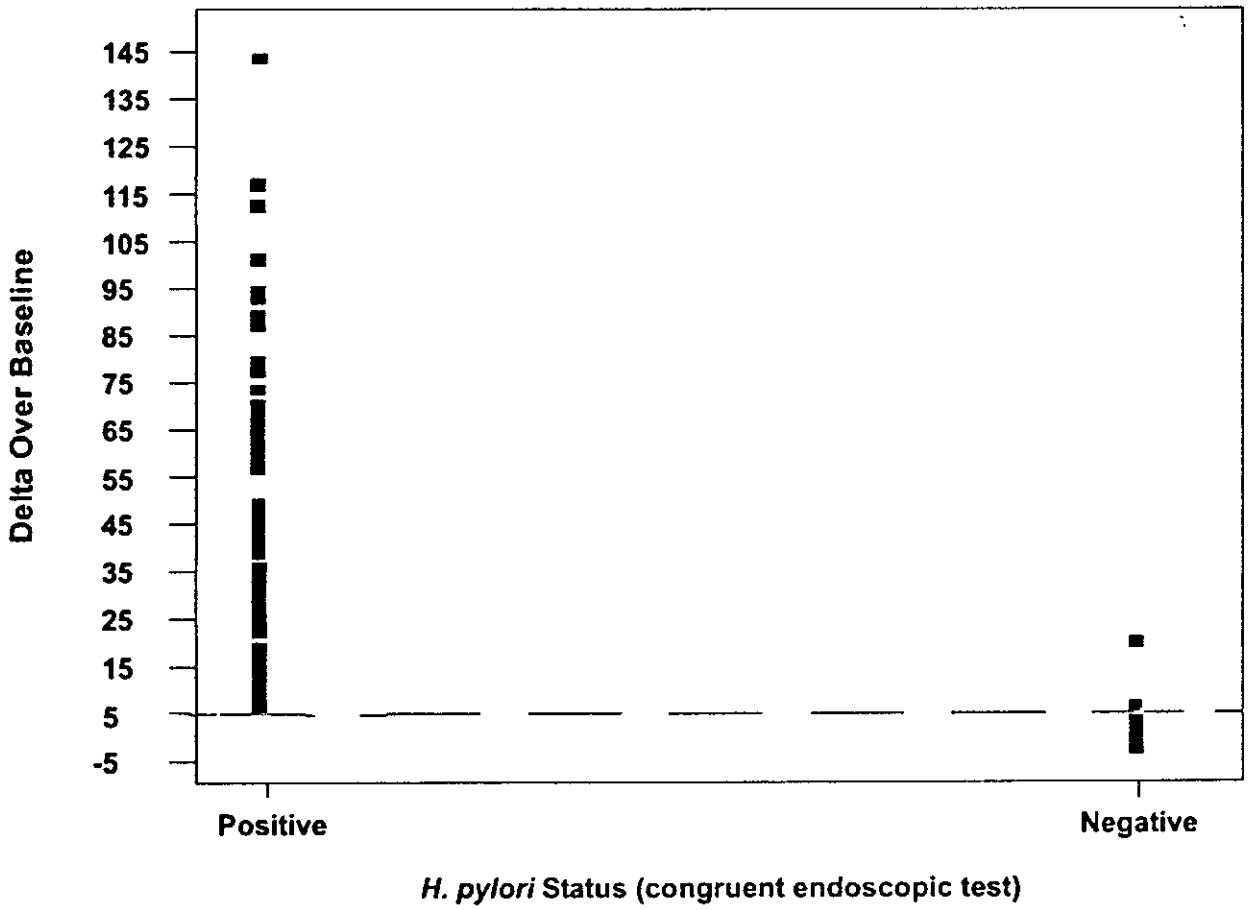
Figure 1 Cutoff for BreathID® Test as Determined in an Initial Clinical Study



The cutoff point was confirmed in a controlled pivotal clinical study. The study consisted of a pre-therapy and post-therapy phase. Patients enrolled in the pre-therapy phase had dyspeptic symptoms, active peptic ulcer disease, or a past history of peptic ulcer disease. To be eligible for the post therapy phase, *H. pylori* positive patients had to be treated for infection 4 weeks prior to enrollment (some patients participated in both the pre-therapy and post-therapy phases). In the pre-therapy phase, 47 patients were infected and 253 were uninfected and congruent results obtained by rapid urease test and histological examination of biopsy tissue were used as the reference standard. In the post-therapy phase, 22 patients were infected and 50 were uninfected. The reference standard was at least one positive by endoscopic test (rapid urease or histology) or Meretek UBT®.

Figure 2 shows graphically the BreathID® Delta Over Baseline results.

Figure 2 Cutoff Point for BreathID® as Determined for Pre-Therapy Patients in the Pivotal Clinical Study



Interpretation of Results

A BreathID® test result of greater than 5 Delta Over Baseline is interpreted as diagnostically positive indicating the presence of urease associated with *H. pylori*.

A BreathID® test result of less than or equal to 5 Delta Over Baseline is interpreted as diagnostically negative indicating the absence of urease associated with *H. pylori*.

The 5 Delta Over Baseline cutoff point applies to both initial diagnosis and post treatment monitoring of *H. pylori* infection.

X. Limitations of the Test

1. Post treatment monitoring of *H. pylori* should not be performed until four weeks after completion of the treatment for *H. pylori* infection. Earlier assessment may give false results.
2. Safety and effectiveness in patients under the age of 18 years have not yet been established.
3. Data is insufficient for recommending the use of this test on patients with total or partial gastroectomy.
4. Data is insufficient to recommend the use of this test on pregnant and lactating women.
5. A correlation between the number of *H. pylori* organisms in the stomach and the BreathID® results has not been established.

Interfering Substances

Potential interfering substances typically found in a patient's breath were tested using the BreathID® System to determine their effect on the test results. The potential sources tested were:

Mouthwash

Chewing gum

Carbonated beverages

Cigarette smoke

Acetone (to simulate the effect of ketone production that may result from some diets)

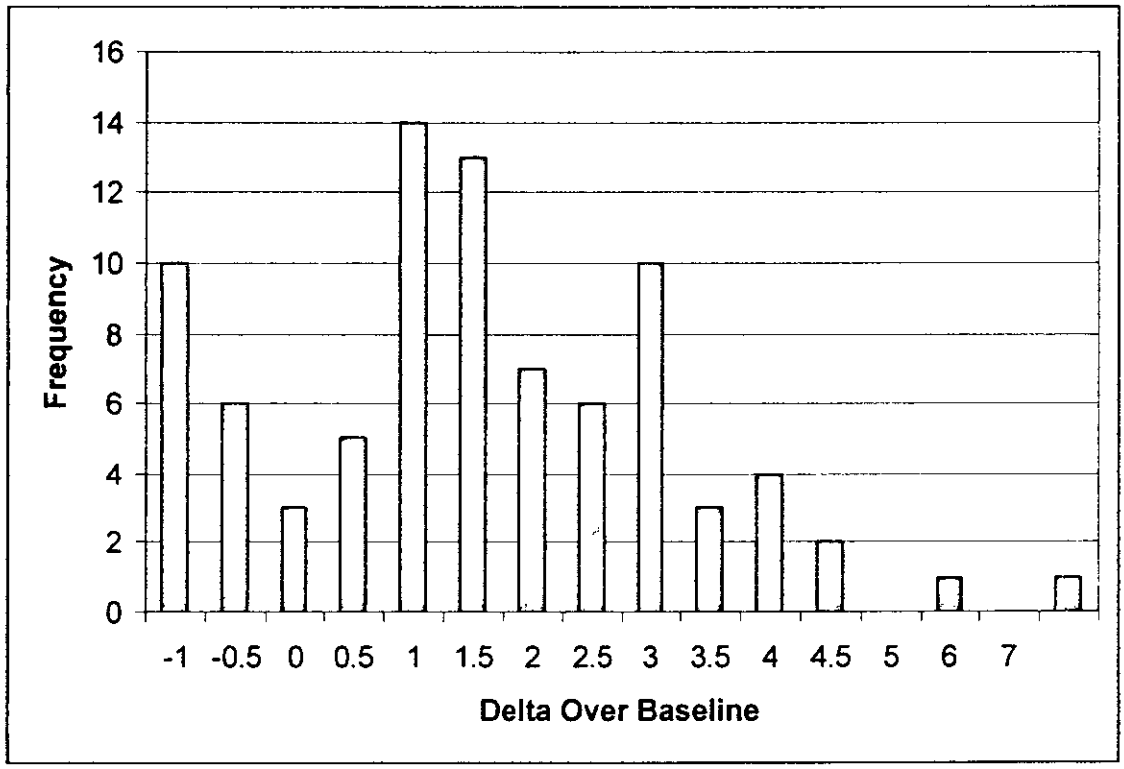
Alcohol ingestion

There was no observation that these substances had any clinically significant influence on the outcome of the test.

XI. Expected Values

Delta Over Baseline values for the BreathID® test were determined in a controlled clinical study of 186 adult asymptomatic and symptomatic patients (101 infected and 85 uninfected) in Israel, using a local reference standard called the Isotope Ratio Mass Spectrometer (IRMS). The range of Delta Over Baseline values for the uninfected patients was determined to be between -1 and 8. A histogram of the distribution of Delta Over Baseline values from uninfected patients is shown in Figure 3 below.

Figure 3 Distribution of Data for Non-Infected Patients as Determined in an Initial Clinical Study



Delta Over Baseline values, as determined in the pivotal clinical study, were used to confirm the initial clinical data. In the pre-therapy phase, there were 47 infected and 253 were uninfected patients. Congruent results obtained by rapid urease test and histological examinations of biopsy tissue were used as the reference standard. In the post therapy phase, 22 patients were infected and 50 uninfected. The reference standard in this phase was at least one positive on either endoscopic test (rapid urease or histology) or Meretek UBT®.

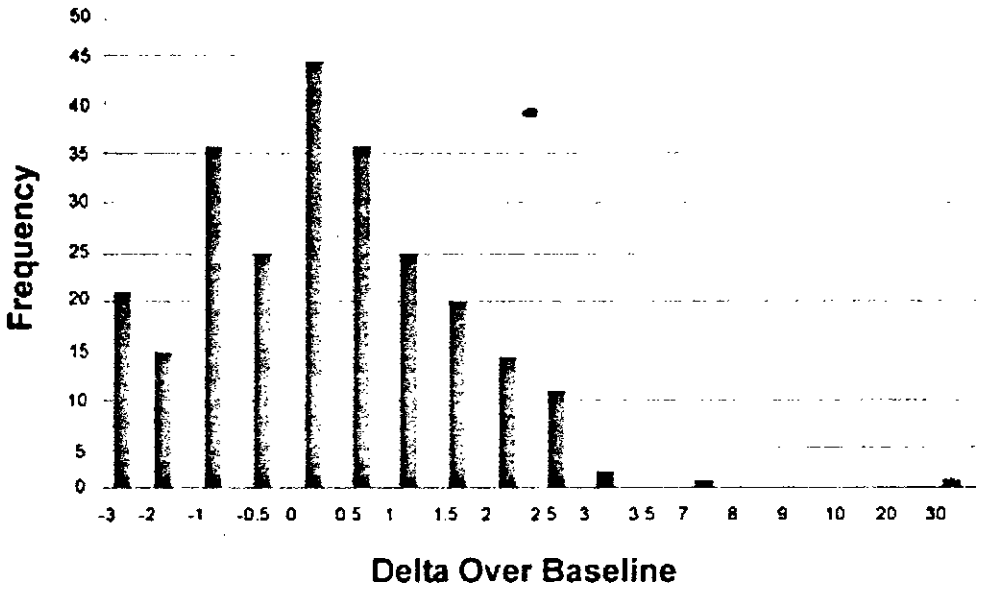
The following values were obtained for the data from the pivotal study:

Upper 97.5% percentile of the Negative patients: 2.245

Lower 2.5% percentile of the Positive patients: 7.212

A histogram of the distribution of Delta Over Baseline values from pre-therapy uninfected (first phase) patients is shown in Figure 4 below.

Figure 4 Distribution of Data for Pre-Therapy Non-Infected Patients as Determined in the Pivotal Study



XII. Performance Characteristics

Reproducibility and Repeatability Results

Tests were conducted to evaluate the reproducibility and repeatability of results when measurements are made by different technicians and/or using different BreathID® devices, or when testing is done on different days.

Reproducibility

Four different gas isotope mixtures were prepared with Delta Over Baseline values of 0, 2.5, 6.5, and 24. Three operators were asked to operate each of three BreathID® devices, in order to measure the Delta Over Baseline values for samples from each of the four batches. The results demonstrated that the standard deviation and overall reproducibility were stable over different batches for both the operator and the devices. The overall reproducibility standard deviation was 0.77, which is less than the natural variability of the Delta Over Baseline measurement.

Repeatability

Three patients (one *H. pylori* negative and two *H. pylori* positive) were measured on three different days. From this limited study, it was concluded that positive and negative subjects maintained their classification with no ambiguity when measured on different occasions.

Patient Results

The relationship between pre- and post-therapy BreathID® test results in patients enrolled in the clinical study was examined. Of the 13 patients who were positive pre-therapy and negative post-therapy and the 3 patients who were positive pre and post-therapy, none had a borderline result post-therapy. The post-therapy negatives patients were close to 0 Delta Over Baseline and the post-therapy positives patients were well above the 5 Delta Over Baseline threshold.

Method Comparison in Clinical Trials

Experimental Design

The method comparison data presented here were collected from a prospective, open-label clinical trial designed to assess the sensitivity and specificity of the BreathID® test in determining the status of gastrointestinal infection with *H. pylori* (pre-therapy phase) and to evaluate the ability of the BreathID® system to monitor the efficacy of therapy for *H. pylori* (post-therapy phase).

There were 315 adult pre-therapy patients at two United States hospitals referred for endoscopy because of dyspeptic symptoms, active peptic ulcer disease, or a past history of peptic ulcer disease. There were 77 post–therapy patients, who were positive for infection and who had undergone eradication therapy at least 4 weeks previously. In addition, 19 of these post-therapy patients also participated in the pre-therapy phase.

Patients were evaluated by at least two of four diagnostic methods:

1. Histopathology: Biopsy specimens, fixed with 10% buffered formalin, were cut into 4 mm sections, stained with Giemsa stain and examined by an experienced pathologist.
2. Rapid Urease Test (CLOtest®): Biopsy specimens were tested for urease activity with the CLOtest® according to the instructions in the package insert.
3. Meretek UBT® Breath Test for *H. pylori* (post-therapy only): The Meretek UBT® was performed according to the instructions in the package insert.
4. Oridion BreathID® test: The Oridion BreathID® test was performed in accordance with the procedures described in the package insert.

Results

Method comparison results are presented in two-way contingency tables.

The exact binomial distribution was used to calculate the lower and upper limits of the 95% confidence intervals of the performance statistic.

Pre-Therapy

Table 1 and Table 2 compare the BreathID® to rapid urease test and histological exam, respectively. In Table 3, the BreathID® is compared to congruent results from the two biopsy-based methods (rapid urease test and histological exam).

Table 1 Comparison of BreathID® Test to Rapid Urease Test (Clotest®)* Pre-Therapy

	BreathID® Test		
CLOtest®	Positive	Negative	Total
Positive	50	0	50
Negative	2	259	261
Total	52	259	311

*Four patients were missing rapid urease test or BreathID® test results.

Relative sensitivity: 100% [95% CI (94.2, 100)]

Relative specificity: 99.2% [95% CI (97.3, 99.9)]

Table 2 Comparison of BreathID® Test to Histology* Pre-Therapy

	BreathID® Test		
Histology	Positive	Negative	Total
Positive	47	2	49
Negative	6	251	257
Total	53	253	306

*Nine patients were missing histology or BreathID® test results

Relative sensitivity: 95.9% [95% CI (86.0, 99.5)]

Relative specificity: 97.7% [95% CI (95.0, 99.1]

Table 3 Comparison of BreathID® Test to Congruent Endoscopic Tests Pre-Therapy

	BreathID® Test		
Congruent Endoscopic Tests	Positive	Negative	Total
Positive	47	0	47
Negative	2	251	253
Total	49	251	300

**H. pylori* positive is defined as positive rapid urea test and positive histology. *H. pylori* negative is defined as negative rapid urea test and negative histology.

Sensitivity**: 100% [95% CI (92.5, 100)]

Specificity**: 99.2% [95% CI (97.2, 99.9)]

**These calculations of sensitivity and specificity do not include 15 patients. In five of these patients, results obtained from the rapid urease test and histology did not match and in 10 of these patients at least one of the three tests was missing.

Post Therapy

Table 4 compares the BreathID® to congruent results from the two biopsy based methods (rapid urease test and histological exam) or urea breath test (Meretek UBT®).

Table 4 Comparison of BreathID® Test to Endoscopic Tests or Meretek UBT® Post Therapy

	BreathID® Test		
Endoscopic Tests or Meretek UBT®*	Positive	Negative	Total
Positive	21	1	22
Negative	0	50	50
Total	21	51	72

**H. pylori* positive is defined as at least one positive on either of the endoscopic tests or Meretek UBT®.

Percent agreement with positive patients: 95.5%

Percent agreement with negative patients: 100%

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