# DOCUMENT INFORMATION PAGE

## DARRTS COMMUNICATION

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| **Application #(s):** | NDA 21-314/S-004 |
| **Communication Type:** | Correspondence |
| **Communication Group:** | sNDA Action |
| **Communication Name:** | Approval |
| **Communication ID:** | COR-SNDAACTION-05 |
| **Drafted by:** | CLD 10.23.14 |
| **Clearance History by:** | FVLeSane/10-27-14; SNambiar 10.28.14 |
| **Finalized:** | |
| **Filename:** | |
| **Use Statement:** | Use to notify applicant of an approval action for a supplemental application that includes changes to the labels or labeling |
| **Notes:** | USE "sNDA Approval [OTC ONLY]" template for Over-the-Counter sNDA Approvals<br>USE COR-SNDAACTION-06 FOR sNDA CMC APPROVALS<br>USE COR-SNDAACTION-09 FOR sNDA TENTATIVE APPROVALS<br><br>If supplement approval also fulfills a PMR/PMC, this letter will need to be double-coded as PMR-PMC Fulfilled. |

Version: DARRTS 04/30/2014

# END OF DOCUMENT INFORMATION PAGE

**The letter begins on the next page.**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-314/S-004

**SUPPLEMENT APPROVAL**

Exalenz Bioscience, Inc.
c/o Exalenz Bioscience, Ltd.
Attention: Larry Cohen
2414 Morris Ave., Suite 201
Union, NJ 07083

Dear Mr. Cohen:

Please refer to your Supplemental New Drug Application (sNDA) dated September 3, 2013, received September 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BreathID System $^{13}$C-Urea Breath Test.

We acknowledge receipt of your amendment dated September 16, 2014.

The September 16, 2014, submission constituted a complete response to our June 6, 2014, action letter.

This "Changes Being Effected" supplemental new drug application provides for changes to the **WARNINGS and PRECAUTIONS, DESCRIPTION** and **SHELF LIFE** and **STORAGE** sections of the labeling.

## APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your September 16, 2014, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described

at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

**REPORTING REQUIREMENTS**

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 Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

# Package Insert

## IDkit: Hp™ for Exalenz BreathID® Hp System

## Breath Test for Detection of *H. pylori*

**SECTION 1. PACKAGE INSERT**

This package insert includes information for conducting the ***H. pylori*** test using ***BreathID® Hp Breath Test System*** for analysis with the Breath Test Kit, IDkit: Hp™ ONE.

The following are trademarks of Exalenz Bioscience Ltd.: Exalenz™, MCS™, IDcircuit™, IDkit: Hp™, and BreathID®.

All reference to Exalenz in this document refers to the company Exalenz Bioscience Ltd.

Note: *No license, expressed or implied, is granted under any patents of Exalenz Bioscience Ltd.*

**SECTION 2. INTENDED USE**

The Exalenz BreathID® Hp System is intended for use to continually and non-invasively measure changes in the $^{13}CO_2/^{12}CO_2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori* (*H. pylori*) infection in the stomach. The Exalenz BreathID® Hp System is indicated for use as an aid in the initial diagnosis and post treatment monitoring of *H. pylori* infection in adult patients. The Exalenz BreathID® Hp System consists of the IDkit: Hp™ ONE and the BreathID® Hp test device.

The device is for use by trained health care professionals. To be administered under a physician's supervision.

**SECTION 3. SUMMARY AND EXPLANATION**

Since the initial identification of *H. pylori* in the early 1980s [1], the management of upper gastrointestinal disease has changed dramatically. "*Helicobacter pylori* is now recognized as an important pathogen and a causal 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 approaches for obtaining a sample for testing: invasive and non-invasive. The first invasive test method requires an endoscopic gastric biopsy. The tissue collected from the biopsy is then examined in a laboratory by microbiological culture of the organism, direct detection of urease activity in the tissue, 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. The second invasive test is a serological test; this requires a blood sample which is used to detect serum antibodies to *H. pylori*. The disadvantage of this test is that it is difficult to distinguish between positive active infections and past exposure to infection, and therefore it is not a conclusive indicator of current *H. pylori* infection.

$^{13}$C-urea breath tests provide a non-invasive 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 and after the oral ingestion of $^{13}$C-enriched urea. This establishes the baseline ratio of $^{13}CO_2/^{12}CO_2$ and the post ingestion ratio of $^{13}CO_2/^{12}CO_2$ in order to determine the Delta Over Baseline[1] (change in the $^{13}CO_2/^{12}CO_2$ ratio).

**SECTION 4. PRINCIPLES OF THE EXALENZ BREATHID® BREATH TEST**

The Exalenz BreathID® non-invasive breath test is a diagnostic test that analyzes a breath sample before and after ingestion of $^{13}$C-enriched urea; it is used to identify those patients with *H. pylori* infection.

The Exalenz BreathID® breath test is performed as follows: a 75 mg $^{13}$C-urea tablet and 4.3 g Citrica Powder are dissolved in water, and the resulting solution is ingested by the patient. The presence of the Citrica creates an acidic environment in the stomach and also delays the transfer of the ingested solution to the duodenum. These two characteristics facilitate the decomposition of the urea by *H. pylori*, if present. Thus, 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 fast. Therefore, the cleavage of urea by the *H. pylori* urease that produces the $^{13}CO_2$ occurs immediately after the solution is ingested and enables immediate detection of increased $^{13}CO_2$ in the exhaled breath of *H. pylori*-positive patients. In the case of *H. pylori*-negative patients, the $^{13}$C-urea does not produce $^{13}CO_2$ in the stomach because there are no human enzymes that can decompose the urea in the stomach.

**4.1.** DESCRIPTION OF THE MODE OF OPERATION OF THE BREATHID® Hp DEVICE

The test begins with the collection of a baseline breath sample. The patient breathes normally while the BreathID® Hp device collects samples through the IDcircuit™ nasal cannula. The IDcircuit™ extracts moisture and patient secretions from the breath samples to provide accurate $CO_2$ readings, and the device measures the $^{13}CO_2/^{12}CO_2$ ratio of the baseline measurement. The patient then ingests a test drink consisting of $^{13}$C-urea tablet 75 mg and 4.3 g of Citrica Powder (4g citric acid).

While the patient continues to breathe normally, the BreathID® Hp device continually and non-invasively samples the patient's breath (via the cannula) 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 display screen while the test continues. The graph shows multiple points that allow the physician to identify the change in the DOB of the $^{13}CO_2/^{12}CO_2$ ratio in response to the administered $^{13}$C-urea. Once the BreathID® Hp device has collected enough data to determine whether or not a patient is *H. pylori*-positive, (i.e. the graph passes the threshold unambiguously), it automatically ends the test and prints out the results.

**SECTION 5. REAGENT**

**5.1.** DESCRIPTION OF THE $^{13}$C-UREA DIAGNOSTIC COMPONENT

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

The 75 mg $^{13}$C-urea component is supplied as a tablet in a sealed pouch. The 4.3 g of Citrica Powder (4 g citric acid [3,4,5], aspartame, and Tutti Frutti flavoring) 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 supplied tablet 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°C). It has the following chemical formula: $^{13}CH_4N_2O$.

**5.2** WARNINGS AND PRECAUTIONS

1. For in vitro diagnostic use only. The $^{13}$C-urea tablet and Citrica Powder are dissolved in a glass of water and the resulting solution is taken orally as part of the diagnostic procedure.
2. Phenylketonurics: Contains Phenylalanine, 84 mg per dosage unit of Citrica Powder.
3. In the case of accidental overdose – drink water and call the physician.
4. A negative result does not rule out the possibility of *H. 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 up to five minutes. However, if more substantial particulate matter is still present after five minutes of mixing, the solution should not be used, and a new kit should be opened.

**5.3.** MIXING THE $^{13}$C-UREA TABLET

1. Dissolve the Citrica and the $^{13}$C-enriched urea tablet in 150 to 200 ml (5.1 to 6.8 oz) of tap water in a single drinking cup of at least 236 ml (8 oz) in capacity.
2. Stir thoroughly with the provided straw for a few minutes, until 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 five minutes of stirring, discard the solution and repeat the procedure with a new kit.*

**5.4.** 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: the $^{13}$C-urea tablet and the Citrica Powder. Do not use either of these components beyond the expiration date stated on the respective labels.

**5.5.** PURIFICATION OR TREATMENT

Purification or treatment for the $^{13}$C-urea tablet is not required prior to use.

**5.6.** INSTABILITY OR DETERIORATION

There are no known physical, biological, or chemical indications of instability or deterioration for the $^{13}$C-urea tablet.

**SECTION 6. INSTRUMENTS**

For detailed information on the BreathID® Hp device, reference the Operator's Manual contained within the BreathID® Hp Package.

**6.1** USE AND FUNCTION OF BREATHID® HP SYSTEM

The Exalenz BreathID® Hp System is intended for use to continually and non-invasively measure changes in the $^{13}CO_2/^{12}CO_2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori* (*H. pylori*) infection in the stomach. The Exalenz BreathID® Hp System is indicated for use as an aid in the initial diagnosis and post treatment monitoring of *H. pylori* infection in adult patients. The Exalenz BreathID® Hp System consists of the IDkit:Hp™ ONE and the BreathID® Hp test device.

The device is for use by trained health care professionals. To be administered under a physician's supervision.

**6.2** INSTALLATION PROCEDURES

The BreathID® Hp software is installed in the BreathID® Hp device upon delivery. To setup the BreathID® Hp:

1. Make sure the power on/off switch is OFF
2. Connect the power cable to the AC socket located on the back panel of the device.
3. Connect the power cable to a properly grounded outlet. It is recommended that you connect the power cable to an uninterrupted power supply (UPS) that supports 100-240 VAC, 50/60 Hz, 750VA
4. Insert the printer paper as shown in the Operator's Manual.

For detailed set-up instructions, reference the Operator's Manual provided in the BreathID® Hp Package.

**6.3** PRINCIPLE OF OPERATION

The Exalenz BreathID® non-invasive breath test is a diagnostic test that analyzes a breath sample before and after ingestion of $^{13}$C-enriched urea; it is used to identify those patients with *H. pylori* infection.

The Exalenz BreathID® breath test is performed as follows: a 75 mg $^{13}$C-urea tablet and 4.3 g Citrica Powder are dissolved in water, and the resulting solution is ingested by the patient. The presence of the Citrica creates an acidic environment in the stomach and also delays the transfer of the ingested solution to the duodenum. These two characteristics facilitate the decomposition of the urea by *H. pylori*, if present. The $^{13}CO_2$ is absorbed into the blood and then exhaled in the breath. Absorption and distribution of $^{13}CO_2$ is fast. Therefore, the cleavage of urea by the *H. pylori* urease that produces the $^{13}CO_2$ occurs immediately after the solution is ingested and enables immediate detection of increased $^{13}CO_2$ in the exhaled breath of *H. pylori*-positive patients.

For detailed information on the principle of operation of the BreathID® Hp device, refer to section 4.

**6.4** PERFORMANCE CHARACTERISTICS

A single center, one-arm, blinded, comparative study was conducted to demonstrate the clinical equivalence of the modified BreathID® Hp System compared to the original BreathID® System. The study included a total of 79 consecutive evaluable adult subjects. The breath test was performed according to the standard procedure and routine clinical practice while the subject was connected simultaneously to both the original BreathID® device and the modified BreathID® Hp device via two standard cannulae. The outcome measures of both devices were used for the comparison. The following percent agreements were determined:

- Percent agreement with positive patients: 100% x 17/17 = 100% [95% CI (81.6, 100)]
- Percent agreement with negative patients: 100% x 60/62 = 96.8% [95% CI (89.0, 99.1)]
- Overall percent agreement: 100% x (17+60)/79 = 97.5% [95% CI (91.2, 99.3)]

A detailed description of the performance characteristics of the modified BreathID® Hp device is provided in section 12.

**6.5** OPERATING INSTRUCTIONS

Detailed instructions on the operation of the BreathID® Hp device are provided below in section 8 and in the Operator's Manual provided in the BreathID® Hp Package.

**6.6** CALIBRATION PROCEDURE

Calibration is performed by diluting pre-dose patient breath or operator breath into five different concentrations within an absolute maximum concentration range. The device uses these five concentrations to determine the systematic error of the system and to ensure that the estimated systematic error is below a specified value. If the systematic error is not below the specified value, the device prompts the user to contact Exalenz for repair or replacement.

For a detailed description of the calibration procedure, refer to section 8.3 or the Operator's Manual.

**6.7** OPERATIONAL PRECAUTIONS AND LIMITATIONS

The following precautions and limitations are applicable to the BreathID® Hp device:

1. A negative result does not rule out the possibility of *H. 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.
2. A false positive test may (rarely) occur due to urease associated with other gastric spiral organisms observed in humans such as Helicobacter heilmanni.
3. A false positive test could occur in patients who have achlorhydria.
4. 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.
5. To ensure accurate performance and prevent device failure, do not expose the BreathID® Hp device to conditions beyond those specified in the Operator's Manual.
6. To avoid entanglement, carefully attach the IDcircuit to the patient.
7. To ensure patient safety, place the device on a stable, flat surface such as a table or desk.
8. Place the device in a location with ample room for ventilation.
9. Do not open or tamper with the device.
10. The operator is required to follow all on-screen instructions.
11. Do not tamper with device software
12. Do not use in the presence of flammable gases or anesthetics.
13. Do not pull on the IDcircuit.
14. Do not clean or sterilize the IDcircuit. The IDcircuit is intended for single patient use only. Dispose of the IDcircuit according to standard operating procedures or local regulations regarding the disposal of contaminated medical waste.
15. Do not spray or pour any liquid on the device or its components.
16. Do not use any caustic or abrasive cleaners on the device.
17. Do not place any object or material anywhere on the device.
18. U.S. Federal Law restricts this device to sale by, or on the order of, a physician or healthcare provider.

The above precautions and limitations are also provided in the Operator's Manual supplied with the BreathID® Hp Package.

**6.8** HAZARDS

The following hazards are applicable to the BreathID® Hp device:

1. Do not open the cover panels. There are no user-serviceable parts inside. There is a risk of electrical shock.
2. The BreathID® Hp is to be serviced by qualified personnel, certified by Exalenz.
3. The device is not suitable for use in the presence of a flammable anesthetic mixture together with air, oxygen or nitrous oxide.

The above hazards are also provided in the Operator's Manual provided in the BreathID® Hp Package.

**6.9** SERVICE AND MAINTENANCE

Service and maintenance information is provided in the Operator's Manual.

**SECTION 7. SPECIMEN COLLECTION AND PREPARATION**

**7.1.** PATIENT PREPARATION

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

The patient should have fasted at least one hour before administering the solution. The patient should not have taken antimicrobials, proton pump inhibitors or bismuth preparations within two weeks prior to administering the test.

**7.2.** ADDITIVES AND PRESERVATIVES

The BreathID® Hp System does not require any additives, preservatives, etc. to maintain the integrity of the breath sample.

**7.3.** INTERFERING SUBSTANCES

Potentially interfering substances typically found in a patient's breath were tested using the original 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

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

**7.4.** BREATH SAMPLE HANDLING INSTRUCTIONS

The analysis of the breath sample is conducted in real-time; therefore, there are no instructions for the storage, handling or shipping for the breath sample.

**SECTION 8. PROCEDURE**

**8.1.** MATERIALS

A single BreathID® IDkit: Hp™ ONE is provided to perform the Breath Test.

Each IDkit: Hp™ ONE for the Exalenz BreathID® Hp Breath Test System contains:

- One tablet of 13C-enriched urea, 75 mg.
- One packet of 4.3 g (4 g citric acid, aspartame, Tutti Frutti flavoring) of Citrica Powder.
- One IDcircuit™ nasal cannula.
- One straw for stirring and drinking.

*Materials Needed But Not Provided:*

- A drinking cup with a capacity of eight ounces (236 ml) or greater.
- Tap water.

**8.2.** STEP-BY-STEP PROCEDURE

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

**For performing the BreathID® *H. pylori* test, use the IDkit: Hp™ ONE single-use kit.**

1. Before opening the kit, verify that the entire package is intact.
2. Ensure that the BreathID® Hp device is activated and the status is **Ready**. The status appears on the top right of the screen.
3. Follow the screen instructions
4. Connecting the IDcircuit™:
   I. Take the IDcircuit™ out of its bag and slide the tubing sleeve down as far as it will go. Gently place the cannula tips into the patient's nostrils, and place the cannula tubing over the ears, as shown in Figure 1.
   II. Slide the tubing sleeve up towards the neck to fit comfortably under the chin.
   III. Connect the IDcircuit™ to the BreathID® Hp device by twisting the orange connector at the free end of the cannula clockwise until it is secured into the dedicated socket of the BreathID® Hp device.
   IV. Verify that the IDcircuit™ is not twisted or kinked and that the cannula tips are in the nostrils. Ensure that the IDcircuit™ cannula tips moldings are positioned inwards.
   V. Press on the START button on the touch screen to proceed. The baseline values will be measured by the BreathID® Hp device and the results will be shown on the screen.
5. Preparing the test drink:

Note: *Administer the test drink within two hours of preparation, as this is the maximal time for maintaining solution stability.*

   I. Dissolve the Citrica Powder and the $^{13}$C -enriched urea tablet in 5.1 to 6.8 oz (150 to 200 ml) of tap water in a single drinking cup of at least eight ounces (236 ml) in capacity.
   II. Stir thoroughly with the provided straw for a few minutes, until the Citrica Powder and the $^{13}$C-urea tablet are completely dissolved.

Note: *Tiny particles may remain visible after thorough mixing. However, if more substantial particulate matter is still present after five minutes of stirring, discard the solution and repeat the procedure with a new kit.*

6. Administering the test drink and starting measurement:

Note*: Do not administer the drink until prompted by the screen instructions on the device (this makes certain that the baseline sample has been collected properly).*

   I. Ensure that the patient drinks the solution through the straw.
   II. The patient must drink the solution within two minutes and consume the entire amount.
   III. After the patient finishes drinking the solution, press the **Continue** button on the touch screen to proceed.

7. Measurement:

   The BreathID® Hp device continually analyzes the trend of measured results. When the device determines that the final value will be positive or negative, i.e. greater or less than 5 Delta Over Baseline, it will automatically end the test and print out the results. The breath sample is analyzed in real-time by the BreathID® Hp device, therefore the stability of the final breath sample will not affect the outcome of the results.

8. 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 all other used components of the kit, according to standard operating procedures or local regulations for the disposal of used 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.*

9. Printing Results:
   I. 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 Patient ID (if entered), date, time, test number and Delta Over Baseline value of the last point measured.
   II. Tear off the printed results and fill in additional patient data as required.

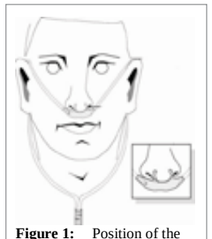

**Figure 1:** Position of the IDcircuit™

**8.3.** CALIBRATION

The calibration stability of the BreathID® Hp system is ensured by the Exalenz proprietary $^{12}CO_2$ and $^{13}CO_2$ Isotope Specific Infrared (ISIR) lamps. 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). 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. This will ensure accurate readings in both negative and positive samples.

In addition, quality checks as described below in section 8.4 are performed by the BreathID® Hp device after every 25 tests in order to ensure that the system performs within established limits, and calibration is performed if required.

Refer to the BreathID® Hp Operator's Manual for a complete description of the calibration procedure.

**8.4.** QUALITY CONTROL

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

However, to ensure correct functioning of the BreathID® Hp in the field, a self test is required once every 25 breath tests. BreathID® Hp will automatically perform a self test after 25 tests are completed, during the baseline measurement phase of the next patient test.

This procedure confirms that the system is functional and is performing within specifications.

Complete operating information including appropriate quality control activities is provided in the BreathID® Hp Operator's Manual.

**SECTION 9. TEST RESULTS**

**9.1.** 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® Hp device software.

**9.2.** CALCULATION OF RESULTS

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

**9.3.** DETERMINATION OF THE CUTOFF POINT

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

The Delta Over Baseline cutoff point was determined to be five in a controlled study of 186 adult asymptomatic and symptomatic patients (101 infected and 85 uninfected). The study was conducted in Israel using a local reference standard called the Isotope Ratio Mass Spectrometer (IRMS). The cutoff point was evaluated by determining the original BreathID® test result (DOB) threshold at which positive and negative patients, as determined by the Isotope Ratio Mass Spectrometer, were best distinguished. Figure 2 shows the BreathID® test cutoff point graphically, which distinguishes *H. pylori*-positive and negative patients.

[1] *Delta Over Baseline is defined as: $DOB = (^{13}CO_2^{(n)}/^{12}CO_2^{(n)} - {}^{13}CO_2^{(0)}/{}^{12}CO_2^{(0)})*1000)/({}^{13}CO_2^{(PDB)}/^{12}CO_2^{(PDB)})$ where PDB is the standard $^{13}$C/$^{12}$C isotope ratio (=0.0112372). (0) is the baseline measurement and (n) is the measurement of interest.*

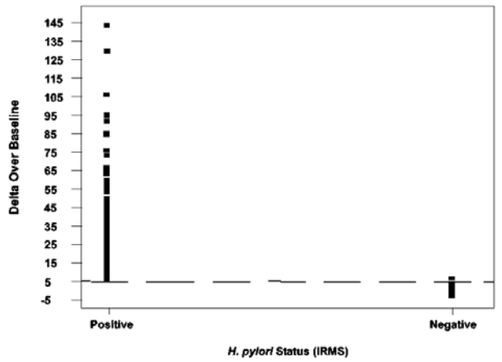


**Figure 2:** Cutoff for BreathID® Test as Determined in an Initial Clinical Study

The cutoff point was confirmed in a controlled pivotal clinical study where 300 subjects were enrolled. 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 four weeks prior to enrollment (some patients participated in both the pre-therapy and post-therapy phases). In the pre-therapy phase, 47 patients were found to be infected and 253 were found to be uninfected. 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 a positive finding by endoscopic test (rapid urease or histology) or urea breath test (UBT). For more details, refer to section 12.

Figure 3 below shows the original BreathID® Delta Over Baseline results.

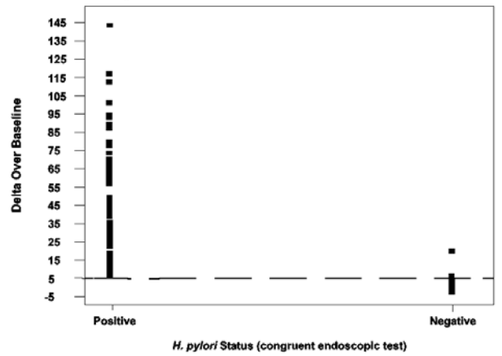


**Figure 3:** Cutoff Point for BreathID® Test as Determined for Pre-Therapy Patients in the Pivotal Clinical Study

**9.4.** 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. For more details, refer to section 12.

**SECTION 10. LIMITATIONS OF THE TEST**

1. Post treatment monitoring of *H. pylori* should be performed after at least four weeks of 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 gastrectomy.
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® test results has not been established.

**SECTION 11. EXPECTED VALUES**

Delta Over Baseline values for the original 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 known reference standard called the Isotope Ratio Mass Spectrometer (IRMS) and performed in a local Israeli laboratory. 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 4 below.

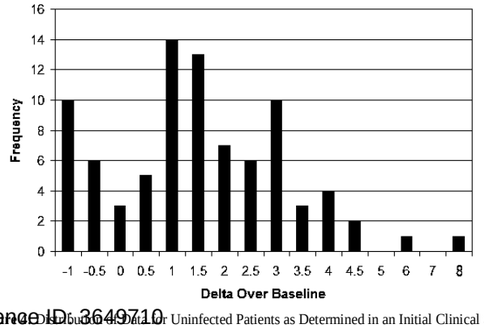


**Figure 4:** Distribution of Data for Uninfected Patients as Determined in an Initial Clinical Study

Delta Over Baseline values, as determined by the original BreathID® in a pivotal clinical study, were used to confirm the initial clinical data.

In the pre-therapy phase, there were 47 infected and 253 uninfected patients. Congruent results obtained by rapid urease test and histological examinations of biopsy tissue were used as the reference standard and were confirmed by the original BreathID® in the 47 infected patients. In the post therapy phase, 22 patients were infected and 50 were uninfected. The reference standard in this phase was at least one positive finding from either an endoscopic test (rapid urease or histology) or by a 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 5 below.

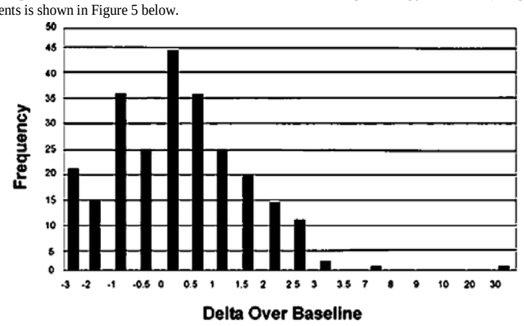


**Figure 5:** Distribution of Data for Pre-Therapy Uninfected Patients as Determined in the Pivotal Study

**SECTION 12. PERFORMANCE CHARACTERISTICS**

**12.1.** ORIGINAL BREATHID® CLINICAL PERFORMANCE RESULTS

12.1.1. PATIENT RESULTS

The relationship between pre- and post-therapy with the original 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 three patients who were positive pre- and post-therapy, none had a borderline result post-therapy. The post-therapy negative patients were close to 0 Delta Over Baseline and the post-therapy positive patients were well above the 5 Delta Over Baseline threshold, again supporting the system coherency.

12.1.2 DIAGNOSTIC METHODS COMPARISON IN CLINICAL TRIAL

***Experimental Design***

The data presented here was collected from a prospective, open-label clinical trial, designed to assess the sensitivity and specificity of the original BreathID® test compared to other methods in determining the status of gastrointestinal infection with *H. pylori* (pre-therapy phase). In addition, the clinical trial was designed to evaluate the ability of the original 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 in the study. There were 77 post–therapy patients who were positive for infection and who had undergone eradication therapy at least four weeks previously. Nineteen of these post-therapy patients participated in the pre-therapy phase as well.

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: Biopsy specimens were tested for urease activity with a FDA-cleared test according to the instructions in its package insert.
3. Urea breath test (UBT) for *H. pylori* (post-therapy only): A FDA-cleared UBT test was performed according to the instructions in its package insert.
4. Exalenz BreathID® test: The Exalenz BreathID® test was performed in accordance with the procedures described in its package insert.

***Results***

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

**Table 1:** Comparison of the Original BreathID® Test to Congruent Endoscopic Tests (RUT and histological exam) 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)]

**Table 2:** Comparison of the Original BreathID® Test to Rapid Urease Test (RUT) Pre-Therapy

| | BreathID® Test | | |
|---|---|---|---|
| **RUT** | **Positive** | **Negative** | **Total** |
| **Positive** | 50 | 0 | 50 |
| **Negative** | 2 | 259 | 261 |
| **Total** | 52 | 259 | 311 |

% positive agreement: 100% [95% CI (94.2, 100)]
% negative agreement: 99.2% [95% CI (97.3, 99.9)]

**Table 3:** Comparison of the Original BreathID® Test to Histology Pre-Therapy

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

% positive agreement: 95.9% [95% CI (86.0, 99.5)]
% negative agreement: 97.7% [95% CI (95.0, 99.1)]

***Post Therapy***

Table 4 compares the results from the original BreathID® to the results from endoscopic tests.

**Table 4:** Comparison of Original BreathID® test to Endoscopic Tests Post-Therapy

| | BreathID® Test | | |
|---|---|---|---|
| **Endoscopic Tests*** | **Positive** | **Negative** | **Total** |
| **Positive** | 6 | 0 | 6 |
| **Negative** | 0 | 20 | 20 |
| **Total** | 6 | 20 | 26 |

** H. pylori positive is defined as positive RUT and positive Histology*
*H. pylori negative is defined as negative RUT and negative Histology*

% positive agreement: 100% [95% CI (60.7, 100)]
% negative agreement: 100% [95% CI (86.1, 100)]

Table 5 compares the results from the original BreathID® to the results from a rapid urease test (RUT).

**Table 5:** Comparison of the Original BreathID® test to RUT Post-Therapy

| | BreathID® Test | | |
|---|---|---|---|
| **RUT** | **Positive** | **Negative** | **Total** |
| **Positive** | 7 | 0 | 7 |
| **Negative** | 0 | 21 | 21 |
| **Total** | 7 | 21 | 28 |

% positive agreement: 100% [95% CI (65.2, 100)]
% negative agreement: 100% [95% CI (86.7, 100)]

Table 6 compares the results from the original BreathID® to the results from a histological exam.

**Table 6:** Comparison of the Original BreathID® test to Histology Post-Therapy

| | BreathID® Test | | |
|---|---|---|---|
| **Histology** | **Positive** | **Negative** | **Total** |
| **Positive** | 6 | 0 | 6 |
| **Negative** | 1 | 20 | 21 |
| **Total** | 7 | 20 | 27 |

% positive agreement: 100% [95% CI (60.7, 100)]
% negative agreement: 95.2% [95% CI (76.2, 99.9)]

Table 7 compares the results from the original BreathID® to the results from a UBT.

**Table 7:** Comparison of the Original BreathID® test to UBT Post-Therapy

| | BreathID® Test | | |
|---|---|---|---|
| **UBT** | **Positive** | **Negative** | **Total** |
| **Positive** | 14 | 1 | 15 |
| **Negative** | 0 | 31 | 31 |
| **Total** | 14 | 32 | 46 |

% positive agreement: 93.3% [95% CI (68.1, 99.8)]
% negative agreement: 100% [95% CI (90.8, 100)]

Table 8 compares the original BreathID® to congruent results from the two biopsy- based methods (rapid urease test and histological exam) or urea breath test.

**Table 8:** Comparison of the Original BreathID® Test to Endoscopic Tests and/ or UBT Post-Therapy

| | BreathID® Test | | |
|---|---|---|---|
| **Endoscopic Tests and UBT*** | **Positive** | **Negative** | **Total** |
| **Positive** | 20 | 1 | 21 |
| **Negative** | 0 | 50 | 50 |
| **Total** | 20 | 51 | 71 |

**H. pylori positive is defined as either positive RUT and positive Histology, or positive UBT.*
*H. pylori negative is defined as either negative RUT and negative Histology, or negative UBT.*

% positive agreement: 95.2% [95% CI (76.2, 99.9)]
% negative agreement: 100% [95% CI (94.2, 100)]

**12.2.** ORIGINAL BREATHID® AND BREATHID® HP COMPARATIVE CLINICAL DATA

***Comparison of BreathID® Hp Test to BreathID® Test***

A single center, one-arm, blinded, comparative study was conducted to demonstrate the clinical equivalence of the modified BreathID® Hp System compared to the original BreathID® System. The Study included a total of 79 consecutive evaluable adult subjects. The breath test was performed according to the standard procedure and routine clinical practice while the subject was connected simultaneously to both the original BreathID® device and the modified BreathID® Hp device via two standard cannulae. The outcome measures of both devices were used for the comparison.

Table 9 compares the modified BreathID® Hp System results to the original BreathID® results for each subject.

**Table 9:** Comparison of the Modified BreathID® Hp Test to the Original BreathID® Test

| | BreathID® Test | | |
|---|---|---|---|
| **BreathID®HP Test** | **Positive** | **Negative** | **Total** |
| **Positive** | 17 | 2 | 19 |
| **Negative** | 0 | 60 | 60 |
| **Total** | 17 | 62 | 79 |

**H. pylori positive is defined as positive on the original BreathID® System.*

% positive agreement: 100% [95% CI (81.6, 100)]
% negative agreement: 96.8% [95% CI (89.0, 99.1)]

**12.3.** REPRODUCIBILITY AND REPEATABILITY RESULTS

Analytical studies were conducted to evaluate the reproducibility and precision (repeatability) of results when measurements are made by different technicians and/or using different BreathID® Hp devices, or when testing is done on different days and at different sites.

**12.4.** REPRODUCIBILITY ANALYTICAL STUDY

Three different accurate gas isotope pairs were used with Delta Over Baseline (DOB) values of 4.5, 5.9, and 15.5 in a bench study. Three operators were asked to operate each of three BreathID® Hp devices in three different sites for five days, in order to measure the DOB values for samples from each of the three batches. The results demonstrated that the standard deviation and overall reproducibility were stable over different batches for both the operator, the devices and between days. The reproducibility standard deviation was less than 0.57 for all batches and the between days and operators standard deviation was less than 0.70, which is less than the natural variability of the DOB measurement. Table 10 summarizes the results of the Reproducibility Analytical Study.

**Table 10:** Results of Reproducibility Analytical Study

| Expected DOB | Parameter | SD Value | 95% CI | CV |
|---|---|---|---|---|
| DOB: 4.5‰ | Reproducibility | 0.524 | 0.483 – 0.573 | 10.9% |
| | Between-Days Reproducibility | 0.533 | 0.455 – 0.624 | 11.0% |
| | Between-Operators Reproducibility | 0.524 | 0.444 – 0.619 | 10.9% |
| DOB: 5.9‰ | Reproducibility | 0.563 | 0.518 – 0.615 | 9.2% |
| | Between-Days Reproducibility | 0.648 | 0.576 – 0.712 | 10.6% |
| | Between-Operators Reproducibility | 0.697 | 0.612 – 0.780 | 11.4% |
| DOB: 15.5‰ | Reproducibility | 0.536 | 0.494 – 0.586 | 3.4% |
| | Between-Days Reproducibility | 0.536 | 0.479 – 0.585 | 3.4% |
| | Between-Operators Reproducibility | 0.538 | 0.485 – 0.591 | 3.4% |

**12.5.** PRECISION ANALYTICAL STUDY (REPEATABILITY)

Three different accurate gas isotope pairs were used with Delta Over Baseline (DOB) values of 4.3, 5.9, and 15.5 in a bench study. The DOB values for samples from each of the three batches were measured on the BreathID® Hp device twice a day for 12 days. The results demonstrated that the standard deviation and overall repeatability were stable over different batches and different days. The repeatability standard deviation was less than 0.69, and the overall between days standard deviation was less than 0.74, which is less than the natural variability of the DOB measurement. Table 11 summarizes the results of the Precision Analytical Study.

**Table 11:** Results of the Precision Analytical Study

| Expected DOB | Parameter | SD Value | 95% CI | CV |
|---|---|---|---|---|
| DOB: 4.3‰ | Repeatability | 0.559 | 0.499 – 0.635 | 12.0% |
| | Between-Days Precision | 0.603 | 0.525 – 0.681 | 12.9% |
| DOB: 5.9‰ | Repeatability | 0.479 | 0.427 – 0.544 | 8.2% |
| | Between-Days Precision | 0.691 | 0.621 – 0.760 | 11.8% |
| DOB: 15.5‰ | Repeatability | 0.689 | 0.615 – 0.784 | 4.4% |
| | Between Days Precision | 0.738 | 0.664 – 0.811 | 4.7% |

**SECTION 13. BIBLIOGRAPHY**


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