IDKIT HP ONE - citric acid anhydrous and 13c urea  
Exalenz Bioscience Ltd.  

Package Insert IDkit:Hp™ for the Exalenz BreathID® System  
BREATH TEST FOR  
DETECTION of H. pylori  

PACKAGE INSERT 005569  
This package insert includes information for conducting the BreathID® H. pylori test for two modes of analysis with two Breath Test Kits:  

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INTENDED USE  
The Exalenz 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 should be used after at least four weeks of H. pylori eradication therapy. For these purposes, the system utilizes Molecular Correlation Spectrometry (MCS™) for the measurement of the ratio of 13CO2 to 12CO2 in breath samples.  

The Exalenz BreathID® System is used to detect and monitor H. pylori infection by measuring changes in the 13CO2 to 12CO2 ratio in a patient's breath following the ingestion of 13C-urea. The Exalenz BreathID® Breath Test System consists of the IDkit:Hp™ kits containing 13C-urea tablet, 75 mg for oral solution and 4.3 g Citrica Powder (4g citric acid) for oral solution; the BreathID® device and the IDcheck™ system quality control accessory. The device is for use by trained healthcare professionals and the test kit is to be administered under a physician's supervision.  

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 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 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 (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. 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 (change in the $^{13}$CO$_2$ / $^{12}$CO$_2$ ratio). (Delta Over Baseline is defined as: \[(^{13}CO_2(N)/^{12}CO_2(N) - \quad^{13}CO_2(0)/^{12}CO_2(0)*1000)/(^{13}CO_2(PDB)/^{12}CO_2(PDB))\] where PDB is the standard $^{13}$C/$^{12}$C isotope ratio (=1.1273%). (0) is the base line measurement and (N) is the measurement of interest.)

**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 and NH$_3$ according to the following equation:

\[
2 \quad^{13}\text{C-urea} + 2 \quad^{12}\text{H}_2\text{O} \quad\longrightarrow \quad H. \quad\text{pylori} \quad\text{urease} \quad\longrightarrow \quad 2 \quad^{13}\text{CO}_2 + 2 \quad\text{NH}_3
\]

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.

**DESCRIPTION OF THE 13C-UREA DIAGNOSTIC COMPONENT**

The diagnostic drug component of the kits 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 13C carbonic acid and is highly soluble in water (1 gram per ml at 25°C). It has the following chemical formula: $^{13}$CH$_4$N$_2$O.

**DESCRIPTION OF THE MODE OF OPERATION OF THE BREATHID® DEVICE**

The BreathID® device can be operated in two pre-selected modes of testing. These are the PATIENT MODE and the BAG MODE as described below.

**PATIENT MODE**

The test begins with the selection of the PATIENT MODE and 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 accurate CO₂ readings, and the device measures the $^{13}$CO₂ / $^{12}$CO₂ 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 citric Powder (4g citric acid).

While the patient continues to breathe normally, the BreathID® device continually and non-invasively samples the patient’s breath (via the cannula) and measures the changes in the $^{13}$CO₂ / $^{12}$CO₂ ratio versus the original baseline sample. These changes are displayed as a graph on the large display screen while the test continues. The graph shows multiple points that allow the physician to identify the change in the DOB of the $^{13}$CO₂ / $^{12}$CO₂ ratio in response to the administered $^{13}$C-urea. Once the BreathID® 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.

**BAG MODE**

The test begins with the collection of normally exhaled breath of the patient into a baseline breath collection bag, which is then sealed. This sample provides the baseline isotope ratio reading. Next, the patient ingests the test drink consisting of dissolved of $^{13}$C-urea tablet, 75 mg and 4.3 g of Citrica Powder (4g citric acid), as in the PATIENT MODE. After 20 minutes, the patient exhales into a post-ingestion breath collection bag, which is subsequently sealed.

The test is performed on the BreathID® device. After selecting BAG MODE, the baseline and then the post-ingestion breath collection bags are connected to the BreathID® device, one after the other. Each bag is separately sampled by the BreathID® device to determine the $^{13}$CO₂ / $^{12}$CO₂ ratio. The values of the ratios obtained are compared in order to determine the Delta Over Baseline (change in the $^{13}$CO₂ / $^{12}$CO₂ ratio between the baseline and the post-ingestion measurements). Once the BreathID® completes measuring the bags, it automatically displays and prints the results. This enables the physician to determine whether a patient is positive or negative for *H. pylori*, based on whether or not the graph passed the threshold line.

**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 (rarely) 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.

**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 kits 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.

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 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.

PROCEDURE

PATIENT MODE

Materials

A single BreathID® IDkit: Hp™ ONE is provided to perform the Breath Test in the PATIENT MODE. Each IDkit: Hp™ ONE for the Exalenz BreathID® Breath Test System contains:

- One Tablet of $^{13}$C-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.

SystemCheck

One SystemCheck accessory is supplied for every 25 units of BreathID® kits, IDkit: Hp™ ONE. The SystemCheck accessory supplied with the BreathID® kits provides quality control for the BreathID® system as described in the Quality Control section. The SystemCheck has an expiration date and shouldn't be used beyond this date as stated on the label.

Materials Needed But Not Provided:

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

Step-by-Step Procedure for the PATIENT MODE

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

For performing the BreathID® H. pylori test in PATIENT MODE, 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® device is activated on PATIENT MODE. The device mode appears on the top corner of the screen.

3. Follow the screen instructions.

4. Connecting the IDcircuit™:
   a. 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.
b. Slide the tubing sleeve up towards the neck to fit comfortably under the chin.
c. Connect the IDcircuit™ to the BreathID® device by twisting the yellow connector at the free end of the cannula clockwise until it is secured into the dedicated socket of the BreathID® device, as shown in Figure 2.
d. 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.
e. Click on the OK button to proceed. The baseline values will be measured by the BreathID® 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.*
   
a. Dissolve the Citrica and the 13C-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.
b. Stir thoroughly with the provided straw for one to two 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.
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).*
   
a. Ensure that the patient drinks the solution through the straw.
b. The patient must drink the solution within two minutes and consume the entire amount.
c. After the patient finishes drinking the solution, press the OK button to proceed.
7. 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, i.e. greater or less than 5 Delta Over Baseline, it will automatically end the test and print out 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:
   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, test number and Delta Over Baseline value of the last point measured.
   b. Tear off the printed results and fill in the patient data.
BAG MODE

Materials

A single BreathID® IDkit: Hp™ TWO is provided to perform the Breath Test in the BAG MODE. Each Exalenz IDkit: Hp™ TWO for the Exalenz BreathID® Breath Test System contains:

- One Tablet of $^{13}$C-enriched urea, 75 mg
- One Packet with 4.3 g (4 g citric acid, aspartame, Tutti Frutti flavoring) of Citrica Powder
- Two differently colored Breath Collection Bags. One bag is silver and marked as BASELINE (T-0) while the other is blue and marked as POST-INGESTION (T-20).
- One mouthpiece.
- Two caps, one for sealing each of the collection bags after the breath collections.
- One straw for stirring and drinking.
- One patient requisition form.
- Two labels (stickers) to be completed with patient and clinical institution information.
- One plastic bag for the filled breath collection bags and the patient requisition form.

SystemCheck

One SystemCheck accessory is supplied for every 25 units of BreathID® IDkit: Hp™ TWO. The SystemCheck accessory supplied with IDkit: Hp™ TWO provides quality control for the BreathID® System, as described in the Quality Control section. The SystemCheck has an expiration date and shouldn't be used beyond this date as stated on the label.

Materials Needed But Not Provided:

- A drinking cup with a capacity of 8 oz (236 ml) or greater.
- Tap water.
Step-by-Step Procedure of the BAG MODE

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

For performing the BreathID® H. pylori test in the BAG MODE, use the IDkit: Hp™ TWO single-use kit.

1. Before opening the kit, verify that the entire package is intact.

2. Open a single-use test kit and fill in the patient requisition form.

3. Prepare the silver-colored Breath Collection Bag(T-0) for the breath test:
   a. Fill in the first label (sticker), marked (T-0).
   b. Take out the silver-colored “Breath Collection Bag - BASELINE (T-0)” for the breath test.
   c. Affix the label (sticker) on the silver Breath Collection Bag (T-0).

4. Preparing the test drink:
   Note: Administer the test drink within two hours of preparation, as this is the maximal time for maintaining solution stability.
   a. Dissolve the Citrica and the 13C-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.
   b. Stir thoroughly with the provided straw for one to two 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, discard the solution and repeat the procedure with a new kit.

5. Baseline bag filing:
   a. Take the silver bag marked as "Breath Collection Bag - BASELINE (T-0)".
   b. Insert the provided mouthpiece approximately halfway into the BASELINE bag.
   c. While holding the bag, instruct the patient to take a deep breath, to hold his breath for 1-2 seconds, and then to forcefully exhale his contained breath into the bag.
   d. Lock the bag tightly with one of the provided caps immediately after it is filled with the patient’s breath. Continue to turn the cap until a clicking sound is heard. This will confirm that the cap is secured and the bag is sealed.

6. Administering the test drink:
   a. Ensure that the patient drinks the solution through the straw.
   b. The patient must drink the solution within two minutes and must consume the entire amount.

7. Prepare the blue “Breath Collection Bag- POST INGESTION (T-20)” for the breath test:
   a. Fill in the label (sticker) marked (T-20), including the time that the second breath sample will be collected (which is time of ingestion + 20 minutes).
   b. Take out the blue Breath Collection Bag for the breath test.
   c. Affix the label (sticker) onto the blue bag.

8. Post-Ingestion bag filling:
   a. Exactly twenty minutes after ingestion (as indicated on the sticker), insert the mouthpiece into the blue bag marked "Breath Collection Bag POST-INGESTION (T-20)"
   b. While holding the bag, the patient is instructed to take a deep breath, to hold his breath for 1-2 seconds, and then to forcefully exhale his contained breath into the bag.
   c. Lock the bag tightly with the remaining cap immediately after it is filled with the patient’s breath. Continue to turn the cap until a clicking sound is heard. This will confirm that the cap is secured and the bag is sealed. Place the two sealed bags and the patient requisition form in the provided plastic bag.

9. Measurement:
   a. Ascertain that the BreathID® device is operating in H. pylori BAG MODE.
   b. The device’s mode of operation appears on the upper corner of the screen. To switch modes of
operation, refer to the Operator’s Manual.
c. Open the plastic bag containing the breath collection bags and patient requisition form.
d. Connect the silver bag marked as "Breath Collection Bag BASELINE (T-0)" via the bag adaptor
   (supplied as part of the accessories kit for IDkit: Hp™ TWO) and the bag connector (supplied as part
   of the Device’s Accessories Box).
e. Prompt the BreathID® to measure the baseline.
f. Disconnect the first bag when instructed to do so by the device and then connect the blue "Breath
   Collection Bag POST-INGESTION (T-20)".
g. The BreathID® automatically computes the Delta Over Baseline (DOB), and after the measurement is
   complete, the device will automatically print the test results. The printout contains the date, time, test
   number and the Delta Over Baseline value.
h. Tear off the printed results, and attach it to the patient requisition form.
i. Disconnect the Breath Collection Bag.
j. Disconnect the Bag Adaptor.

QUALITY CONTROL
The BreathID® 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® 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. However, to ensure correct functioning of the BreathID® in the field,
an accessory labeled SystemCheck is provided for every 25 units of IDkit: Hp™. The BreathID® will
automatically display a request to perform a SystemCheck™ after 25 tests are completed. The
BreathID® device will not continue to function unless the SystemCheck accessory is used as
directed. The SystemCheck quality control is accomplished by introducing a single-use cartridge that
contains a known concentration of CO$_2$ into the device after every 25 breath tests. This procedure
confirms that the BreathID® System is functional and is performing within specifications. Complete
operating information including appropriate quality control activities is provided in the BreathID®

CALIBRATION
The calibration stability of the BreathID® 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 above in the Quality Control section are performed by the
BreathID® device after every 25 tests in order to ensure that the BreathID® System performs within
established limits, and calibration is performed if required. Refer to the BreathID® Operator’s Manual
for a complete description of the SystemCheck and calibration procedure.

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 Delta Over Baseline. Delta Over Baseline is the difference between the Delta value (based on a ratio of $^{13}\text{CO}_2 / ^{12}\text{CO}_2$) in the test specimen and the corresponding 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 betweeny *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 BreathID® test result (DOB) threshold at which positive and negative patients, as determined by the Isotope Ratio Mass Spectrometer, were best distinguished. Figure 3 shows the BreathID® cutoff point graphically, which distinguishes *H. pylori*-positive and negative patients.

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 Meretek UBT®. For more details, refer to the Performance Characteristics section. Figure 4 shows the BreathID® Delta Over Baseline results.
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 the Performance Characteristics section.

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® results has not been established.

INTERFERING SUBSTANCES
Potentially 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

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

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
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 5 below.

Delta Over Baseline values, as determined by the 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 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 the 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 6 below.
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 (BENCH STUDY)

Four different accurate gas isotope mixtures were prepared with Delta Over Baseline values of 0, 2.5, 6.5, and 24 in a bench study. 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 \emph{H. pylori}-negative and two \emph{H. pylori}-positive) were measured on three different days. From this limited observation, it was assumed that positive and negative subjects maintained their classification with no ambiguity when measured on different occasions. Based on this observed trend and in combination with the reproducibility results, it was concluded that the system is very consistent.

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 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.

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 BreathID® test compared to other methods in determining the status of gastrointestinal infection with \emph{H. pylori} (pre-therapy phase). In addition, the clinical trial was designed to evaluate the ability of the BreathID® system to monitor the efficacy of therapy for \emph{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 (CLOtest®): Biopsy specimens were tested for urease activity with the CLOtest® according to the instructions in its package insert.
3. Meretek UBT® Breath Test for \emph{H. pylori} (post-therapy only): The Meretek UBT® 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 1 and Table 2 compare the BreathID® to rapid urease tests and histological exams, respectively. In Table 3, the BreathID® outcome is compared to congruent results from the two endoscopy biopsy-based methods (rapid urease test and histological exam).

Table 1: Comparison of BreathID® Test to Rapid Urease Test (Clotest®)

<table>
<thead>
<tr>
<th>BreathID® Test</th>
<th>Clotest®</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>50</td>
<td>0</td>
<td>Total</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>259</td>
<td>261</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>259</td>
<td>311*</td>
</tr>
</tbody>
</table>

*Four patients out of the 315 were missing either the rapid urease test or BreathID® test results and therefore were not included in the table.
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

<table>
<thead>
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<th>BreathID® Test</th>
<th>Histology</th>
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<tbody>
<tr>
<td>Positive</td>
<td>47</td>
<td>2</td>
<td>49</td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>251</td>
<td>257</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>253</td>
<td>306*</td>
</tr>
</tbody>
</table>

*Nine patients out of the 315 were missing either histology or BreathID® test results and therefore were not included in the table.
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 (Clotest® and histological exam) Pre-Therapy

<table>
<thead>
<tr>
<th>BreathID® Test</th>
<th>Congruent Endoscopic Tests*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>47</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>251</td>
<td>253</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>251</td>
<td>300</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Endoscopic Tests of Meretek UBT®*</th>
<th>BreathID® Test</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
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<tr>
<td>Positive</td>
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<td>1</td>
<td>22</td>
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</tr>
<tr>
<td>Negative</td>
<td>0</td>
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<tr>
<td>Total</td>
<td>21</td>
<td>51</td>
<td>72</td>
<td></td>
</tr>
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</table>

*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%

PATIENT MODE AND BAG MODE EQUIVALENCY

The two sampling modes of the BreathID® are PATIENT MODE sampling (using the continuous measuring of patient's breath before and after ingestion of the test solution*) and BAG MODE sampling (using two breath collection bags to sample patient's breath before and after ingestion of the test solution*). These sampling modes are described in the Procedure section of this Package Insert.

The BreathID® outcome capabilities of these two sampling modes were evaluated and compared in a series of bench tests using accurate gases and in one clinical study, as described below.

*Containing 75 mg $^{13}$C-urea tablet and 4.3 g Citrica Powder.

Non-clinical validation (bench tests)

Objectives:
1. To demonstrate the accuracy and precision of the BAG MODE sampling collection compared to the PATIENT MODE sampling collection ("protocol 1").
2. To demonstrate precision and stability testing of the isotope ratio readings at time 0 and after seven days of storage ("protocol 2").

Methodology:

- Protocol 1: Three different devices were used to assess DOB of the $^{13}$CO$_2$ to $^{12}$CO$_2$ ratio from samples taken from different predetermined DOB in gas sources. These DOB were 0, 5.92, 9.58, 15.5 and ~50. These DOB were assessed by both modes of the BreathID® device: the previous inherent PATIENT MODE and the new inherent BAG MODE. Each assessment was repeated three times, so there were a total of 45 tests for each mode. The order of the experiments was randomly assigned.

- Protocol 2: One device was used to assess DOB of the $^{13}$CO$_2$ to $^{12}$CO$_2$ ratio from samples taken from different predetermined DOB in gas sources. These DOB were 0, 9.5, 15.5 and ~50. Nine collection bags were filled from each of the four sources (total of 36) to be tested at time "0." Another set of 36 collection bags were collected at the same time and stored for seven days, after which they were tested and compared to time "0" for repeatability, in order to evaluate stability of the breath sample in the bag.
In addition (in protocol 2), three collection bags were filled from three sources of 0, 9.5 and 15.5 to complete a set of nine bags. This was repeated twice more, so a total of 27 collection bags were collected in time "0." One set of nine collection bags was tested at time "0" and the other two sets were kept at different temperatures for seven days. One set was kept at 2º-8º Celsius and the second set was kept between 40-50º Celsius. After seven days, the collection bags were tested in the same device. This was done to demonstrate reproducibility.

Criteria for evaluation:
The accuracy and precision of the two modes were evaluated. The mean differences between the DOB as obtained by the device and the true values and their standard deviations were calculated. Mean differences should be near zero if the measurement is accurate.

Statistical methods:
Accuracy was assessed by comparing the measurement to its corresponding known value. Mean differences and 95% confidence intervals were calculated. The standard deviation of the mean difference and its 95% confidence interval were presented as an additional measure of accuracy versus the known constants. Repeatability expresses the precision under the same operating conditions over a short interval of time. Reproducibility expresses the precision between different operating conditions. The 95% confidence intervals for repeatability were calculated using a random effects analysis of variance model using the PROC MIXED procedure. The confidence interval of the reproducibility was calculated with bootstrap methodology using 10,000 simulated samples.

Results:
The overall accuracy of the BAG MODE was 0.11 (95% CI: [-0.91 – 1.13]). This value is similar to the overall accuracy of the PATIENT MODE -0.06 (95% CI: [-0.61 – 0.48]). The repeatability and reproducibility of the measurements assessed with the BAG MODE and PATIENT MODE are similar. Repeatability was 1.07 (95% CI: [0.87 - 1.38]) versus 0.97 (95% CI: [0.70 - 1.66]) and reproducibility 1.22 (95% CI: [0.70 -1.66]) versus 1.05 (95% CI: [0.73 -1.38]), respectively. Again, this demonstrates similar results for both modes. Assessment of the BAG MODE measurements has shown that the overall mean change in DOB measured after seven days is 0.02 (SD=1.21), irrespective of DOB of gas samples; subsequently, it can be reproduced after seven days in storage. Also, the results of the BAG MODE were found to be within the system specification.

Conclusion:
The data provided by these non-clinical experiments demonstrates the overall high agreement between the PATIENT MODE and the BAG MODE performances and the accuracy of the BAG MODE values. Furthermore, the non-clinical testing portrays the high level of precision, repeatability, and reproducibility of the BAG MODE results.

Clinical Validation
Objectives:
To show that the BAG MODE results in human subjects are in very high agreement with the results of the PATIENT MODE.

Methodology:
Validation of the BAG MODE included a clinical study comparing the BAG MODE and the PATIENT MODE applied on the same subjects, which were administered with the test solution of 13C-urea and Citrica as per Clinical protocol number# 4B-CV-409. For evaluation of the BAG MODE, 48 subjects were enrolled in this study.

Statistical methods:
The overall percent agreement between the diagnoses was calculated with a 95% exact confidence interval, sensitivity and specificity of the BAG MODE versus the PATIENT MODE, with their
The mean and standard deviation of the difference between the DOB measurements was calculated together with a 95% confidence interval. A linear regression model was fitted to the DOB value obtained by both modes. The slope and intercept together with their respective 95% confidence intervals were calculated. In addition, a Bland-Altman plot of the mean versus the difference were calculated, and the 95% limits of agreement were calculated together with their respective confidence intervals.

Results:
The overall agreement percentage is 100% (48/48) with a 95% exact binomial CI: [92.6%-100%] sensitivity of the BAG MODE versus the PATIENT MODE. Method diagnosis is 100% (95% exact binomial CI:[87.66%-100%]) and specificity is 100% (95% exact binomial CI:[83.16%-100%]).

Conclusion:
The clinical outcome results obtained by the BAG MODE are essentially the same as those obtained by the PATIENT MODE. Therefore, the two collection modes are considered equivalent and can be used interchangeably for assessing the presence of H. pylori infection with the BreathID® System.

SUMMARY

The above sections of the performance validations of all aspects of the BreathID® System show unequivocally that the BreathID® System can be used with its kits and two sampling modes to determine the DOB (change in the $^{13}$CO$_2$/^$^{12}$CO$_2$ ratio between the baseline and the post-ingestion measurements) and therefore to imply the presence of H. pylori in humans when the DOB is above 5.

REFERENCES


REPRESENTATIVE PACKAGING

See How Supplied section for a complete list of available packages of the IDkit:Hp™ for the Exalenz BreathID® System.
Case containing 25 kits of IDkit:Hp™ ONE

IDkit: Hp™ One
BREATH TEST FOR DETECTION OF H. pylori

Containing:
1 Tablet "C-Urea 75 mg.
1 Packet Citrica 4.3 g.1 IDCircuit™

Refer to Package Insert Prior to Use
To be used with Exalenz BreathID® system only.
The product is supplied non-sterile. For single use only.
Do not attempt to clean, sterilize or reuse. For diagnostic use only.

Reorder No.: V507719
USA Patents 5,657,750; 6,422,240; 6,437,318; 6,463,983; 6,728,729; 6,186,958; 6,656,127; 7,488,229; 7,260,976; 7,063,667; 5,969,357

Manufactured by:
Exalenz Bioscience Ltd.
4 Ha'maayan St.
Modiin, Israel 71700
Tel: +972-8-9737500
Fax: +972-8-9737501
E-mail: contact@exalenz.com

USA Distributor:
Exalenz Bioscience Inc.
1313 N. Market St.
Suite 5100
Wilmington, DE 19801, USA
Tel: 1-888-EXALENZ

Lot#: Exp.:

Exalenz
Breathtaking Solutions

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Kit label for **IDkit: Hp™ ONE**

**IDkit: Hp™ TWO**

**BREATH TEST FOR DETECTION OF H. pylori**

**Containing:**
5 IDkit: Hp™ Breath Test Kits.

**Manufactured by:**
Exalenz Bioscience Ltd.
4 Ha’maayen St.
Modin, Israel 71700
Tel: +972-8-9737500
Fax: +972-8-9737501
E-mail: contact@exalenz.com

**USA Distributor:**
Exalenz Bioscience Inc.
1913 N. Market St.
Suite 5100
Wilmington, DE 19801, USA
Tel: 1-888-EXALENZ

**www.BreathID.com**

**Box containing 5 kits of IDkit: Hp™ TWO**
Kit label for **IDkit:Hp™ TWO**

**Citrica**
(citric acid powder for oral solution) 4.0 g
Refer to Package Insert Prior to Use

**Ingredients:** citric acid, aspartame, tutti-frutti flavor

To be used with Exalenz Bioscience IDkit: Hp™ and BreathID® device only. Not to be sold separately. For diagnostic use only. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

**Phenylketonurics:** Contains 84 mg of phenylalanine per packet of Citrica

Net weight 0.15 oz/4.3 g
P/N: VS07867

**Manufactured by:** TARO Pharmaceutical Industries, Haifa Bay 26110, Israel 70636-0309-0

**For:** Exalenz Bioscience Ltd., Modiin 71700, Israel

**Distributed by:** Exalenz Bioscience Inc., 1313 N. Market Street Suite 5100 Wilmington, DE 19801 Tel: 1-888-EXALENZ

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**13C-Urea**
(13C-urea tablet for oral solution) 75 mg
Refer to Package Insert Prior to Use

To be used with Exalenz IDkit: Hp™ and BreathID® device only. Not to be sold separately. For diagnostic use only. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

**Manufactured by:** TARO Pharmaceutical Industries Ltd, Haifa Bay 26110, Israel 70635-0309-0

**For:** Exalenz Bioscience Ltd, Modiin 71700, Israel

**Distributed by:** Exalenz Bioscience Inc., 1313 N. Market Street Suite 5100 Wilmington, DE 19801 Tel: 1-888-EXALENZ

P/N: 007760

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**IDKIT HP ONE**
citric acid anhydrous and 13c urea kit

**Product Information**

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### Part 1 of 2

**CITRICA**
citric acid anhydrous powder, for solution

### Product Information

**Route of Administration**: ORAL

### Active Ingredient/Active Moiety

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### Product Characteristics

**Color**: Score

**Shape**: Size

**Flavor**: TUTTI FRUTTI (Tutti Frutti Flavor)

**Contains**: Imprint Code

### Marketing Information

**Marketing Category** | **Application Number or Monograph Citation** | **Marketing Start Date** | **Marketing End Date**
------------------------|---------------------------------------------|--------------------------|-----------------------|
NDA                    | NDA021314                                   | 12/28/2009               |                       |
Part 2 of 2

UREA C-13
urea c-13 tablet, for solution

Product Information

Route of Administration
ORAL

Active Ingredient/Active Moiety

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<td>urea c-13</td>
<td>75 mg</td>
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Labeler - Exalenz Bioscience Ltd. (514832786)

Establishment

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<td></td>
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Revised: 9/2011

Exalenz Bioscience Ltd.