4.1 Intended Use

The BreathTek® UBT for H. pylori Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of H. pylori in the human stomach and is indicated as an aid in the initial diagnosis and post-treatment monitoring of H. pylori infection in adults, and pediatric patients 3 to 17 years old. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. For these purposes, the system utilizes an Infrared Spectrophotometer for the measurement of the ratio of 13CO2 to 12CO2 in breath samples, in clinical laboratories and point-of-care settings. The Pediatric Urea Hydrolysis Rate Calculation Application (pUHR-CA), provided as a web-based calculation program, is required to obtain pediatric test results.

The BreathTek UBT Kit is for administration by a health care professional, as ordered by a licensed health care practitioner.

2 Summary and Explanation

Since the isolation of the spiral urease-producing Helicobacter pylori (H. pylori) bacteria in 1983 by Drs. Marshall and Warren, a significant body of evidence has accumulated indicating that the bacteria is an important pathogen in the upper GI tract of humans. H. pylori is associated with a number of GI conditions including chronic gastritis, peptic ulcer disease, and gastric malignancy. Methods available for detecting current infection of the human stomach by H. pylori are generally divided into two (2) general types: Invasive and Non-invasive.

Invasive methods are so named because they include, as a first step, an endoscopy with collection of gastric biopsies ("EGD") followed by histological examination of stained tissue, microbiological culture of the organism, or direct detection of urease activity in the tissue. Biopsy based methods are expensive, entail some patient risk and discomfort and may give false negative results due to sampling errors when colonization of the gastric mucosa is patchy.

Non-invasive methods include serological testing, fecal antigen test, and urea breath test. Several serological tests that detect serum antibodies to H. pylori are commercially available. A positive result with a serologic test cannot distinguish between current infection and past exposure to infection and, therefore, is not a conclusive indicator of current gastrointestinal colonization by H. pylori. Urea breath tests are a non-invasive method for detecting current H. pylori infection.

3 Principle of the BreathTek UBT for H. pylori

3.1 Description of the Pranactin®-Citric Diagnostic Drug Component

The diagnostic drug component of the kit is 13C-urea, a synthetic urea contained in a granulated powder (Pranactin-Citric) for reconstitution with potable water to provide a clear solution for oral administration. The carbon in the drug component is predominantly Carbon-13, a stable, naturally occurring, non-radioactive isotope of carbon; the relative abundance of Carbon-13 is greater than or equal to 99%. Each 3 gram dose of Pranactin-Citric is supplied in a polyethylene-lined foil pouch and contains 75 mg of 13C-urea, citric acid, aspartame and mannitol. 13C-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: CH3N15O. An average adult body normally contains about 9 grams of urea, which is a product of protein metabolism. Urea in the body is referred to as natural isotopic abundance urea since it is composed of 98.9% 12C-urea and 1.1% 13C-urea.

3.2 Principle of the Test

Pranactin-Citric drug product is a component of the BreathTek UBT Kit. Three (3) g of reconstituted Pranactin-Citric containing 75 mg of 13C-urea is ingested by the patient. In the presence of urease associated with gastric H. pylori, 13C-urea ([NH2]13CO2) is decomposed to CO2 and NH3, according to the following equation:

H. pylori urease

\[(NH_2)_2^{13}CO + H_2O + 2H^+ \rightarrow 13CO_2 + 2NH_3\]

The 13CO2 is absorbed in the blood, and then exhaled in the breath. It results in an increase in the ratio of 13CO2 to 12CO2 in a POST-DOSE breath sample taken after the Pranactin-Citric solution was consumed, compared to a BASELINE sample taken before the Pranactin-Citric solution was consumed. Analysis of the breath samples is performed by UBiT®-IR300 Infrared Spectrophotometer or POCON® Infrared Spectrophotometer located at your clinical laboratory and point-of-care settings.

In the absence of gastric H. pylori, the 12C-urea does not produce 13CO2 in the stomach. The ratio of 13CO2 in the POST-DOSE breath sample remains essentially the same as the BASELINE.

3.3 Adjustment of Endogenous CO2 Production with UHR Calculation in Pediatric Patients

The measured difference between the ratios of 13CO2 to 12CO2 values before and after administration of Pranactin-Citric solution is referred to as Delta over Baseline (DOB). DOB is the primary outcome measure reported by BreathTek UBT for pediatric patients. It is known that the measured Delta over Baseline (DOB) is a function of anthropometric variables, which determine the rate of CO2 production.

While the effect of the CO2 production rate is small between adults, it can be significant in pediatric patients. Therefore, in performing the BreathTek UBT on pediatric patients, the primary outcome measure reported for the BreathTek UBT is the UHR. The UHR is calculated as shown below:

\[\text{DOB} \times \text{CO2 Production Rate} = \text{UHR} \times \text{mL/min} = \text{DOB} \times \text{CO2 Production Rate} \times 0.3427\]

4 Warnings and Precautions

4.1 For in vitro diagnostic use only

The Pranactin-Citric solution is taken orally as part of the diagnostic procedure.

4.2 Phenylketonurics: Contains Phenylalanine (one of the protein components of Aspartame). Phenylketonurics restrict dietary phenylalanine.

4.3 A negative result does not rule out the possibility of H. pylori infection. False negative results do occur with this procedure. If clinical signs are suggestive of H. pylori infection, retest with a new sample or an alternate method.

4.4 False negative test results may be caused by:

- Ingestion of proton pump inhibitors (PPIs) within 2 weeks prior to performing the BreathTek UBT. If a negative result is obtained from a patient ingesting a PPI within 2 weeks prior to the BreathTek UBT, it may be a false negative result and the test should be repeated 2 weeks after discontinuing the PPI treatment. A positive result for a patient on a PPI could be considered positive and be acted upon.

- Ingestion of antibiotics, or bismuth preparations within 2 weeks prior to performing the BreathTek UBT.

- Premature POST-DOSE breath collection time for a patient with a marginally positive BreathTek UBT result

- Post-treatment assessment with the BreathTek UBT less than 4 weeks after completion of treatment for the eradication of H. pylori.

4.5 False positive test results may be caused by:

- Urea associated with other gastric spiral organisms observed in humans such as Helicobacter heilmannii.

- Achlorhydria.

- Oral contamination associated with urea containing bacteria especially when not using the straw provided in the BreathTek UBT kit.

4.6 If a positive result is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.

4.7 Hypersensitivity: Patients who are hypersensitive to mannitol, citric acid or Aspartame should avoid taking the drug solution as this drug solution contains these ingredients. Swollen lip and rash were reported in the pediatric clinical studies.

4.8 Risk of Aspiration: Use with caution in patients with difficulty swallowing or who may be at high risk for aspiration due to medical or physical conditions.

4.9 Pregnancy/Lactation: The safety of using the BreathTek UBT kit during pregnancy and lactation is not established.

4.10 For positive test results, the UHR results must be calculated. DOB results in conjunction with Pediatric Urea Hydrolysis Rate Calculation Application (pUHR-CA), provided as a web-based calculation program, is required to obtain pediatric test results. DOB results cannot be used to determine the infection status of pediatric patients.

4.11 Safety and effectiveness has not been assessed in children below the age of 3 years.

5 Adverse Events

5.1 Adults-Postmarketing Experience

During post-approval use of the BreathTek UBT, the following adverse events have been identified: anaphylactic reaction, hypersensitivity, rash, burning sensation in the stomach, tingling in the skin, vomiting and diarrhea. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

5.2 Pediatrics-Clinical Experience

In two clinical studies conducted on 176 (analyzed) pediatric patients ages 3 to 17 years to determine the initial diagnosis and post treatment monitoring of H. pylori infection, the following adverse events were experienced by 21% of these patients were: vomiting (5.1%), oropharyngeal pain (4.5%) to include throat irritation, sore throat, throat burning), nausea (2.3%), restlessness (2.3%), stomach ache/belly pain (1.1%), and diarrhea (1.1%). Most of the adverse events were experienced by the patients within minutes to hours of ingestion of the Pranactin-Citric solution.

In another clinical study comparing the UBT/IR300 and POCON in pediatric patients ages 3 to 17 years, the following adverse events were observed among the 99 subjects enrolled: 2 incidences of headache, 1 incidence of cough, dry mouth and acute upper respiratory infection.

6 Shelf Life and Storage

The BreathTek UBT Kit should be stored at 15°-30°C (59°-86°F). Pranactin-Citric has an expiration date of 18 months.

7 Patient Preparation

7.1 Remind the patient that Pranactin-Citric contains phenylalanine (one of the protein components of Aspartame). Phenylketonurics restrict dietary phenylalanine.

7.2 The patient should have fasted at least 1 hour before administering the BreathTek UBT.

7.3 The patient should not have taken antibiotics, proton pump inhibitors (PPIs), or bismuth preparations within 2 weeks prior to administering the BreathTek UBT. If PPIs are used within 2 weeks of BreathTek UBT testing, false negative test results may occur, and the test should be repeated 2 weeks after discontinuation of PPI treatment. A positive result for a patient on PPI could be considered positive and be acted upon.

7.4 The effect of histamine 2-receptor antagonists (H2RAs) may reduce urea activity on urea breath tests.

7.5 Use of antacids does not appear to affect the accuracy of the BreathTek UBT.

7.6 For administration by a healthcare professional only. Do not provide this kit to the patient for self-administration.

7.7 If repeat testing is needed, BreathTek UBT can be administered again on the following day.

8 Procedure for Collecting Breath Samples Using BreathTek UBT Kit, for Analysis by Infrared Spectrophotometer

8.1 Materials

8.1.1 Materials provided

Each single patient BreathTek UBT Kit contains:

- One (1) “How To” guide with One (1) patient p-UHR card
- Test instructions
- One (1) pouch of Pranactin-Citric powder (3 g)
- One (1) 6 gram Pranactin-Citric kit
- A set of four (4) self-adhesive bar-code stickers. All bar-codes should bear the same number.
- Two (2) breath collection bags, one (1) blue bag for the BASELINE sample and one (1) pink bag for the POST-DOSE sample
- One (1) sample transport bag
8.2 Step-By-Step Procedure

8.2.1 Open the BreathTek UBT Kit, which should contain all the materials listed in Step 8.1.1. Label

8.2.2 Prepare the Pranactin-Citric solution

8.2.3 Collect the BASELINE breath sample according to the following procedure:

8.2.4.4 Discard the straw after the patient has finished drinking the drug solution. a. Tear off the top of the packet and carefully empty the contents into the drinking cup provided, making sure to transfer all of the contents by tapping on the bottom of the pouch. b. Set the timer for 15 minutes. The patient should sit quietly and should not eat, drink or smoke during the 15 minute interval. Breath sample may be collected no later than 30 minutes POST-DOSE.

8.2.5 After 15 minutes have elapsed, pick up the pink breath collection bag. Collect the POST-DOSE breath sample according to the procedure described in Steps 8.2.3 b through 8.2.3 d.

8.2.6 Store the specimens at 15°-30°C (59°-86°F) until analysis is performed.

8.2.7 Perform breath sample analysis within 7 days of breath sample collection. If desired, the web-based UBiT-IR300 or POCone Infrared Spectrophotometer provides the interpretation of the DOB result on the test strip.

8.2.8 Interpretation of Results for Adults

8.2.9 Interpretation of Results for Pediatrics

9 Quality Control

10 Test Results

10.1 Adults

10.1.1 The Test Method

10.1.2 Calculation of Results

10.1.3 Determination of the Cutoff Point

10.2 Pediatrics

10.2.1 The Test Method

10.2.2 Calculation of Results

10.2.3 Determination of the Cutoff Point

10.2.4 Interpretation of Results for Pediatrics

10.2.5 Interpretation of Results for Adults

**DOB cutoff value for Meretek UBT was determined to be 2.4 in this study.** Distribution of Meretek UBT DOB values in infected and uninfected groups in this study is shown in Figure 1a. The Meretek UBT was subsequently validated in clinical trials of patients with documented duodenal ulcer disease (see Section 13.4).

For the BreathTek UBT, the DOB cutoff values was determined to be 2.4 in a controlled study of 26 infected and 23 uninfected adult volunteers. Test subjects were judged to be in acceptable health based on the results of a medical history and physical examination and demonstrated no uncontrolled clinically significant abnormality other than, for some, symptoms of peptic ulcer. The Meretek UBT was used as the reference standard. The range of BreathTek UBT DOB values for the uninfected group was determined to be 0.0 to 1.0. The cutoff value was calculated by determining the BreathTek UBT result level at which negative and positive subjects were best distinguished by co-optimization of relative sensitivity and specificity. Distribution of BreathTek UBT DOB values in infected and uninfected groups in this study is shown in Figure 1b.

The 2.4 cutoff point for the BreathTek UBT was validated in an independent study by retrospective analysis of Clinical Field Trial data collected on 145 H. pylori negative and 105 H. pylori positive test subjects using the original Meretek UBT as a reference (see Section 13.4.2).

**Figure 1a. Data Distribution before the Cutoff for Meretek UBT**

**Figure 1b. Data Distribution before the Cutoff for BreathTek® UBT**

**Figure 2: Data Distribution and Cutoff for UHR**

**Figure 3: Data Distribution and Cutoff for BreathTek® UBT**
11 Limitations of the Test

11.1 The BreathTek UBT should not be used until 4 weeks or more after the end of treatment for eradication of H. pylori as earlier post-treatment assessment may give false negative results.

11.2 The performance characteristics for initial diagnosis and post-treatment monitoring for pediatric patients < 3 years of age have not been established for this test.

11.3 The specimen integrity of breath samples and reference gases stored in breath bags under ambient conditions has not been determined beyond 7 days.

11.4 A correlation between the number of H. pylori organisms in the stomach and the BreathTek UBT result has not been established.

11.5 Do not use DOB to determine the H. pylori positive or negative results in pediatric patients. Use the web-based pUHR-CA to calculate the UHR to obtain pediatric test results.

11.6 The web-based pUHR-CA to calculate the UHR to obtain pediatric test has only been tested with Firefox and Internet Explorer.

12 Expected Values

12.1 Adults

12.2 Pediatrics

11.5 Do not use DOB to determine the H. pylori positive or negative results in pediatric patients. Use the web-based pUHR-CA to calculate the UHR to obtain pediatric test results.

Go to: https://BreathTekKits.com

11.6 The web-based pUHR-CA to calculate the UHR to obtain pediatric test has only been tested with Firefox and Internet Explorer.

13 Performance Characteristics

13.1 The primary performance measure for clinical validation of both the Meretek UBT and the BreathTek UBT is a composite reference method consisting of histology and H. pylori culture of endoscopically-obtained gastric biopsies as well as a urease detection assay.

13.2 Analytical Performance Characteristics for the UBT-I300 Infrared Spectrophotometer. Refer to the Instruction Manual for the instrument.

13.3 Analytical Performance Characteristics for the POCone Infrared Spectrophotometer. Refer to the Instruction Manual for the instrument.

13.4 Clinical Performance in Clinical Trials for Adults

13.4.1 Comparison of Meretek UBT with the Composite Reference Method in the Adult Population

a. Experimental Design

The clinical performance data presented here were collected from a prospective, cross-over clinical field trial designed to validate the BreathTek UBT test procedure and to examine the effect of pre-test fasting time on test performance. The study included 252 adult test subjects from Houston and Galveston, Texas. Subjects were judged to be in acceptable health based on the results of a medical history and physical examination and demonstrated no uncontrolled clinically significant abnormality other than, for some, symptoms of dyspepsia. Test subjects were tested for H. pylori infection using the Meretek UBT according to established procedure and with the BreathTek UBT under differing conditions of pre-test fasting times. Otherwise, no special instructions were given to subjects beyond those listed in the step-by-step procedures for administration of the Meretek UBT and BreathTek UBT. To minimize potential bias due to test order, the sequence of urea breath tests administered to each subject was randomized. All breath tests were administered to a given individual within 14 days of one another, most often and at a minimum, on successive days.

b. Results

It was demonstrated in the field trial that the BreathTek UBT may be administered at any time beyond 1 hour after consuming solid and/or liquid food.

Point estimates of Percent Agreement of the BreathTek UBT with Meretek UBT positive and negative results are listed in the contingency table (Table 3). The comparative method for determining the true diagnosis was the predicate device (Meretek UBT) rather than endoscopic methods. The exact binomial distribution was used to calculate the lower and upper limits of the 95% confidence intervals of the performance statistics. The confidence intervals are entered in parentheses following the point estimate of the statistic.

Table 3. Comparison of BreathTek UBT (≥1-hour fast) with Meretek UBT

<table>
<thead>
<tr>
<th>Meretek UBT Results</th>
<th>BreathTek UBT Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td>Positive</td>
<td>105</td>
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<tr>
<td>Negative</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
</tr>
<tr>
<td>Percent Agreement</td>
<td>99.5% [95% CI: 94.9, 100.0]</td>
</tr>
</tbody>
</table>

Percent Agreement with Meretek UBT positive subjects: 99.5% [95% CI: 94.9, 100.0]
Percent Agreement with Meretek UBT negative subjects: 99.8% [95% CI: 96.2, 100.0]

13.4.3 Comparison of Gas Isotope Ratio Mass Spectrometry (GRIMS) and UBT-I300 Infrared Spectrophotometry Method in the Adult Population

A multi-center prospective clinical trial was conducted to compare the UBT-I300 method with the traditional GIRMS method. The study included a total of 320 adult test subjects enrolled at 4 physicians’ office (POL) settings and at a clinical laboratory. The results of the clinical trial are provided in the Instructional Manual for the UBT-I300 Infrared Spectrophotometer (refer to the Application Note, 13C-Urea Breath Test using the UBT-I300 Infrared Spectrophotometer System).

Table 4 shows the percent agreement of the UBT-I300 results as compared to the GIRMS method. Overall agreement was excellent at 99.06 percent.

Table 4. Agreement of UBT-I300 and GRIMS for 13C urea breath test

<table>
<thead>
<tr>
<th>GIRMS Results</th>
<th>UBT-I300 Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>115</td>
</tr>
<tr>
<td>Negative</td>
<td>116</td>
</tr>
<tr>
<td>Total</td>
<td>231</td>
</tr>
</tbody>
</table>

Percent Overall Agreement: 99.06% [95% CI: 97.35, 99.74]
Percent Positive Agreement: 98.29% [95% CI: 94.26, 99.70]
Percent Negative Agreement: 99.51% [95% CI: 97.49, 99.97]

13.4.4 Comparison of UBT-I300 and POCone Infrared Spectrophotometry Methods in the Adult Population

A multi-center, prospective study was conducted to compare the POCone Infrared Spectrophotometer to the UBT-I300 Infrared Spectrophotometer for measuring 13CO2 enrichment in breath. The study included a total of 220 adult test subjects enrolled at 5 physicians’ office laboratory (POL) and point of care (POC) settings. The results of the clinical trial are provided in the Instruction Manual for the POCone Infrared Spectrophotometer (refer to the Application Note, 13C-Urea Breath Test using the POCone Infrared Spectrophotometer System).

* Composite reference method includes histology, urease detection test and culture for post-treatment monitoring.
13.5.3 Comparison of UBIT-IR300 and POCone Infrared Spectrophotometry Methods in the Pediatric Population

a. Experimental Design

A multi-center, prospective study was conducted to compare the POCone to the UBIT-IR300 in measuring $13^\text{CO}_2/12^\text{CO}_2$ ratio in breath samples when used together with the BreathTek UBT Kit and the pH-URA-C in identifying $H.\text{ pylori}$ infection in pediatric subjects. The study included a total of 99 pediatric subjects ages 3 – 17 years enrolled at two pediatric gastroenterology clinics and one general pediatric clinic. The breath samples were analyzed and UHRA calculated either at the point-of-care setting or at a central laboratory. Twenty (20) subjects who tested positive at the initial visit returned for post-treatment monitoring test 4 weeks or longer after a course of $H.\text{ pylori}$ eradication therapy.

b. Results – Comparison of the POCone (UHR) to the UBIT-IR300 (UHR)

Table 8 shows the percent agreement of the POCone results with the UBIT-IR300 results in 95 evaluable cases as part of the initial diagnosis. Overall agreement was 100 percent.

Table 8. Agreement of POCone and UBIT-IR300 for the UHRA-C

<table>
<thead>
<tr>
<th>POCone Results</th>
<th>UBIT-IR300 Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POCone</strong></td>
<td><strong>UBIT-IR300</strong></td>
</tr>
<tr>
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<td>Positive</td>
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<td></td>
<td>24</td>
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<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

Percent Overall Agreement: 100% [95% CI: (96.2, 100.0)]

14 Bibliography


15 Name and Place of Business

The BreathTek UBT for $H.\text{ pylori}$ Kit is manufactured for Medical Device Division of Otsuka America Pharmaceutical Inc., 2440 Research Boulevard, Rockville, MD 20850. For additional information, please call 1.888.637.3835 or visit www.BreathTek.com.

16 Trademarks

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