

# SUMMARY OF SAFETY AND EFFECTIVENESS

## I. GENERAL INFORMATION

Device Generic Name: Urea Breath Test (UBT) and Calculation Software

Device Trade Name: BreathTek UBT for *H. pylori* Kit (BreathTek UBT Kit)  
and Pediatric Urea Hydrolysis Rate Calculation  
Application (pUHR-CA), Version 1.0

Applicant's Name and Address:

Otsuka America Pharmaceutical, Inc. (OAPI)  
2440 Research Blvd.  
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Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P100025

Date of FDA Notice of Approval: February 22, 2012

Expedited: Not Applicable

Please note that this SSED only discusses the pediatric population studied, 3 to 17 years old. For information pertaining to adult population, please refer to the BreathTek UBT Kit currently cleared for use in adult patients under 510(k) premarket notification, K014225, and the Pranactin-Citric is approved under NDA 20-586/S-004. The age group of 18 to 21 years old was not included in the current PMA application for both the initial diagnosis and the post monitoring treatment as this was cleared for use in 510(k) K014225.

## II. INDICATIONS FOR USE

The BreathTek UBT for *H. pylori* Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of urease associated with *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 4 weeks following completion of therapy. For these purposes, the system utilizes an Infrared Spectrophotometer for the measurement of the ratio of  $^{13}\text{CO}_2$  to  $^{12}\text{CO}_2$  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 prescribed by a physician.

\*The BreathTek UBT Kit is currently cleared for use in adult patients under 510(k) premarket notification, K014225, and the Pranactin-Citric is approved under NDA 20-586/S-004.

### III. CONTRAINDICATIONS

None

### IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the BreathTek UBT for *H. pylori* Kit and Pediatric Urea Hydrolysis Rate Calculation Application (pUHR-CA), Version 1.0 labeling.

### V. DEVICE DESCRIPTION

The BreathTek UBT Kit 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. The BreathTek UBT Kit is a combination product that includes a diagnostic drug component. The BreathTek UBT Kit is currently cleared for use in adult patients under 510(k) premarket notification, K014225, and the Pranactin-Citric is approved under NDA 20-586/S-004. This PMA application is submitted to expand the indication for use as an aid in the initial diagnosis and post-treatment monitoring in pediatric patients 3 to 17 years old and for the use of the Pediatric Urea Hydrolysis Rate Calculation Application, (pUHR-CA), Version 1.0, as a computational aid to obtain pediatric test results.

In the BreathTek UBT Kit, the pouched Pranactin-Citric drug product containing  $^{13}\text{C}$ -urea is reconstituted with water and then ingested by the patient. The  $^{13}\text{C}$ -urea is decomposed by urease associated with gastric *H. pylori* forming  $^{13}\text{CO}_2$  and  $\text{NH}_4^+$ . The  $^{13}\text{CO}_2$  is absorbed into the blood, and then exhaled in the breath. The result of the BreathTek UBT is provided as the Delta Over Baseline (DOB) which is the difference between the ratio of  $^{13}\text{CO}_2/^{12}\text{CO}_2$  in the post-dose sample and the corresponding ratio in the baseline sample. Analysis of the breath samples from adult patients is performed by either the UBiT-IR300 or POcone Infrared Spectrophotometer; both instruments have been cleared for marketing under Premarket Notification Submissions K013371 and K041148, respectively. A DOB result  $\geq 2.4$  is interpreted as positive for *H. pylori* infection, and a result  $< 2.4$  is interpreted as negative for *H. pylori* infection in adult patients.

The cutoff value defining a positive result from the DOB does not take  $\text{CO}_2$  production into account. Because production of  $\text{CO}_2$  varies according to age, gender, weight, and height, and because the cutoff value of 2.4 calculated for adults is likely to overestimate infection in pediatric patients, the pUHR-CA is used to recalculate the results based on DOB. Thus, the pUHR-CA provided as a web-based application on the internet is used to calculate the pediatric test result where the DOB result is converted into a UHR metric result. The UHR metric result correlates to a test result as *H. pylori* positive ( $\geq 10.0 \mu\text{g}/\text{min}$ ) or *H. pylori* negative ( $< 10.0 \mu\text{g}/\text{min}$ ). For these purposes, the pUHR-CA utilizes the DOB result obtained from

the patient's breath samples analyzed on the UBiT-IR300 Infrared Spectrophotometer, and the age, gender, height and weight of the pediatric patient. DOB results cannot be used to determine the infection status in pediatric patients. Pediatric breath samples can only be analyzed on the UBiT-IR300 Infrared Spectrophotometer.

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

There are several other alternative methods for the detection of *H. pylori* in human specimens. These include; an endoscopy procedure to perform histology, immunohistochemical stains, culture, and urease tests, serological assays to detect immunoglobulins A, G, or M antibodies to *Helicobacter pylori*, stool antigen test and other urea breath tests however there are no FDA approved breath test for pediatric use. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

## **VII. MARKETING HISTORY**

The BreathTek UBT Kit is marketed in the United States and Mexico for use in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

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 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.

Pediatrics-Clinical Experience: During the pediatric clinical studies the following adverse events were reported: vomiting, oropharyngeal pain, (to include throat irritation, sore throat, throat burning), nausea, restlessness, stomach ache/belly pain, and diarrhea. Most of the adverse events were experienced by the patients within minutes to hours of ingestion of the PranaActin-Citric solution.

For the specific adverse events that occurred in the pediatric clinical studies, please see Section X below.

## **IX. SUMMARY OF THE PRECLINICAL STUDIES**

All cutoff studies were performed using the BreathTek UBT for *H. pylori* Kit and Pediatric Urea Hydrolysis Rate Calculation Application (pUHR-CA), Version 1.0 on the UBiT-IR 300 Infrared Spectrophotometer. The web-based pUHR-CA converts DOB to the UHR result in pediatric patients. The calculation incorporates

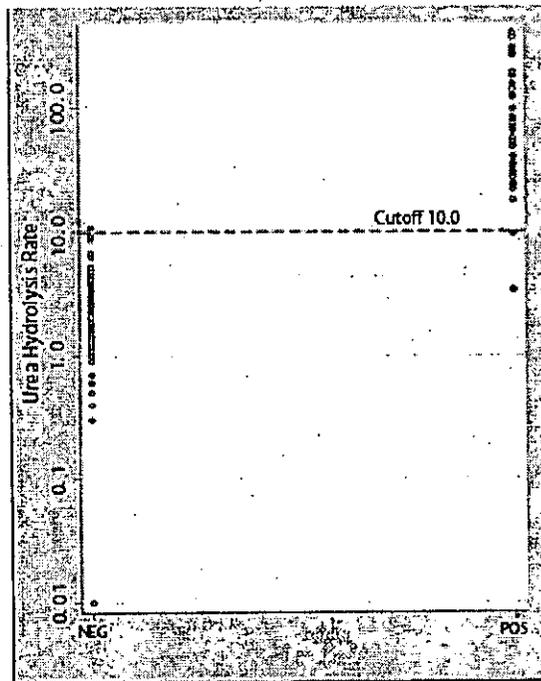
the patient's anthropometric data (i.e., age, gender, height, and body weight) to calculate the CO<sub>2</sub> production rate in that patient. The UHR is calculated as shown below:

$$\text{UHR } (\mu\text{g}/\text{min}) = \text{DOB} \times \text{CO}_2 \text{ Production Rate} \times 0.3427$$

Determination of the Cutoff Point: The cutoff point study was conducted to establish the clinical cutoff for interpretation the BreathTek UBT test result as positive or negative.) UHR values from pediatric patients were first established in a group of 312 asymptomatic preschool and school-age children aged 1 - 10 years in the Houston, Texas, area.<sup>1</sup> A UHR cutoff value was determined to be 10.0  $\mu\text{g}/\text{min}$ .

This UHR cutoff value was subsequently validated in two multi-center, controlled clinical studies of dyspeptic children aged 3 - 17 years using the BreathTek UBT Kit and the UBiT-IR300 Infrared Spectrophotometer. *H. pylori* infection was established with an endoscopic composite reference method criteria for specimen classification determination consistent with the FDA guidance.<sup>2,3</sup> Of the 176 analyzed study subjects, the range of UHR values was 0.0 - 10.9  $\mu\text{g}/\text{min}$  for the 128 uninfected children and 3.4 - 403.8  $\mu\text{g}/\text{min}$  for the 48 infected children. The distribution of the UHR values is shown in Figure 1. Note that the UHR scale is logarithmic; therefore, in displaying negative UHR values on a logarithmic scale, values between -5 and 0 were assigned a value of 0.01.

**Figure 1: Data Distribution and Cutoff for UHR**



Interpretation of Results for Pediatrics: A UHR value of  $\geq 10 \mu\text{g}/\text{min}$  is interpreted as diagnostically positive indicating the presence of urease associated with *H. pylori*. A UHR value of  $< 10 \mu\text{g}/\text{min}$  is interpreted as diagnostically negative indicating the absence of urease associated with *H. pylori*. The same UHR cutoff

value applies to both initial diagnosis and post-treatment monitoring of *H. pylori* infection in children. The web-based pUHR-CA program provides the interpretation of the UHR result on the output of the calculation. Go to: <https://pUHRCA.Otsuka-U.com/pUHR-CA> to use the web-based pUHR-CA program.

## X. SUMMARY OF PRIMARY CLINICAL STUDIES

### Clinical Performance in Clinical Trials for Initial Diagnosis in Pediatric Patients

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of urea breath collection in pediatric population with BreathTek UBT for the qualitative detection of urease associated with *H. pylori* in the human stomach in the U.S. under IDE # G000317 and NDA # 20-586/S-004. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

#### a. Experimental Design

The clinical performance data were collected from a multi-center, open-labeled study designed to compare the BreathTek UBT with endoscopic methods for the initial diagnosis of *H. pylori* in pediatric population. Subjects were symptomatic pediatric patients 3 to 17 years old undergoing diagnostic upper endoscopy at the determination of their treating pediatric gastroenterologist. Study enrollment was based on esophagogastroduodenoscopy (EGD) performed on each subject in proximity to the administration of the BreathTek UBT kit. The study enrolled 206 pediatric patients at five (5) U.S. investigational sites (New Orleans, Louisiana, Miami, Florida, Houston, Texas, Huntington, West Virginia, and Detroit, Michigan), of which 176 subjects were evaluable for analysis. The reasons for exclusion are shown in Table 1 below.

**Table 1: Reasons for Subject Exclusion\***

Reason	Number excluded
EGD not done	10
Culture and Histology not done	1
BreathTek UBT not done	3
Invalid UBT Results	10
Prohibited medication Use**	4
Consent withdrawn	1
Lost Records	1
Total	30

\* There were more than 1 reason for some subjects; however, they are counted once in this table.

\*\* Proton pump inhibitor use N=3 subjects; Antibiotic use N=1.

Adverse events were reported in 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 these patients: 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.

**b. Results – Clinical Performance of BreathTek UBT UHR to the Composite Reference Method Criteria**

The primary endpoint analysis was conducted to determine the sensitivity and specificity of the BreathTek UBT UHR to the composite reference method criteria for the 176 evaluable cases. Table 2 demonstrates the diagnostic performance of the BreathTek UBT (expressed as UHR) compared to the composite reference method criteria in pediatric patients aged 3-17 years old.

**Table 2: Clinical Performance of Composite Reference Method Criteria and BreathTek UBT (UHR) in Pediatric Patients for Initial Diagnosis**

Endoscopic Composite Reference Method	<sup>13</sup> C-UBT UHR							
	Age 3-5 Years		Age 6-12 Years		Age 13-18 Years		All Age Groups Combined	
	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg
Infected	3	0	21	0	22	2	46	2
Not Infected	0	17	0	62	1	48	1	127
Sensitivity (95% CI)	100.0 (29.2, 100.0)		100.0 (83.9, 100.0)		91.7 (73.0, 99.0)		95.8 (85.7, 99.3)	
Specificity (95% CI)	100.0 (80.4, 100.0)		100.0 (94.2, 100.0)		98.0 (89.0, 100.0)		99.2 (95.7, 100.0)	

**Clinical Performance in Clinical Trials for Post-Treatment Monitoring in Pediatric Patients**

**a. Experimental Design**

This study was a multi-center, open-labeled study designed to compare the BreathTek UBT with endoscopic methods for the post-treatment monitoring of *H. pylori* in pediatric population. Pediatric patients 3 to 17 years old who enrolled in this study had participated in the initial diagnosis study described above, and were diagnosed by upper endoscopy to be infected with *H. pylori* using the composite reference method criteria (e.g., histology, culture and rapid urease test).

The study enrolled 22 pediatric patients at three (3) U.S. investigational sites (Houston, Texas, Detroit, Michigan, and Huntington, West Virginia) of which 20 subjects were evaluable for analysis. The reasons for data exclusion were due to invalid UBT results and EDG was not performed.

The primary outcome variable of the BreathTek UBT was the UHR in comparison to the endoscopic findings of the composite reference method criteria. To determine the infection status following eradication therapy, these criteria were interpreted to include test results for all three *H. pylori* testing methods (histology, culture, rapid urease test). Results for all three *H. pylori* testing methods were available for all of the 20 evaluable cases. The primary endpoint analysis was conducted to determine the sensitivity and specificity of the BreathTek UBT (UHR) to the composite reference method criteria for the 20 evaluable cases.

**b. Results—Comparison of BreathTek UBT (UHR) to the Composite Reference Method Criteria**

The observed sensitivities for UHR when compared to the composite reference method criteria is 83.3%, and the observed specificity is 100% (Table 3). Because of the small sample size, the results, including the 95% confidence intervals around the sensitivity and specificity, should be interpreted with caution.

**Table 3: Clinical Performance of Composite Reference Method Criteria and BreathTek UBT UHR in Pediatric Patients for Post-Treatment Monitoring**

		<sup>13</sup> C-UBT UHR	
		N=20	
		Pos	Neg
Composite Reference Method Criteria	Infected	5	1
	Eradicated	0	14
Sensitivity		83.3% [95% CI: (40.2, 99.2)]	
Specificity		100% [95% CI: (77.0, 100.0)]	
PPV		100%	
NPV		93.3%	

## **XI. PANEL MEETING RECOMMENDATIONS AND FDA'S POST-PANEL ACTION**

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the FDA Microbiology Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Safety Conclusions**

The adverse effects (AE) of the device are based on data collected in clinical studies conducted to support PMA approval as described above. The AE profile noted in pediatrics in this study is similar to the AE profile noted in the post approval period (rash, burning sensation in the stomach, tingling in the skin, vomiting and diarrhea), and similar to what is expected from the drug component composition. The approved labeling reflects the frequency of overall AEs regardless of causality, and the frequency of AEs thought to be related to the administration of the breath test. In addition, labeling indicates the similarity of AE profile in children and adults.

### **B. Effectiveness Conclusions**

Performance characteristics of BreathTek UBT for *H. pylori* Kit and Pediatric Urea Hydrolysis Rate Calculation Application (pUHR-CA), Version 1.0 were similar across age groups, race and study sites, and similar in males and females. The primary endpoint analysis was conducted to determine the sensitivity and specificity of the BreathTek UBT for *H. pylori* Kit and Pediatric Urea Hydrolysis Rate Calculation Application (pUHR-CA), Version 1.0 to the composite reference method criteria for the 176 evaluable cases in study 1 for the initial diagnosis. The observed sensitivities for UHR when compared to the composite reference method criteria is 95.8%, and the observed specificity is 99.2%.

The primary endpoint analysis was conducted to determine the sensitivity and specificity of the BreathTek UBT for *H. pylori* Kit and Pediatric Urea Hydrolysis Rate Calculation Application (pUHR-CA), Version 1.0 to the composite reference method criteria for the 20 evaluable cases in study 2 for post-treatment monitoring. The observed sensitivities for UHR when compared to the composite reference method criteria is 83.3%, and the observed specificity is 100%.

Study endpoints were met for both studies and determined to be acceptable.

### **C. Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The submitted clinical studies have shown that the BreathTek UBT for *H. pylori* Kit and Pediatric Urea Hydrolysis Rate Calculation Application (pUHR-CA), Version 1.0, when compared to the composite reference method, has similar ability to aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in pediatric patients 3 to 17 years old.

### **XIII. CDRH DECISION**

CDRH issued an approval order on February 22, 2012. The final conditions of approval are cited in the approval order.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

### **XIV. APPROVAL SPECIFICATIONS**

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

### **XV. REFERENCES**

1. Klein PD, Malaty HM, Czinn SJ, Emmons SC, Martin RF, and Graham DY. Normalizing Results of <sup>13</sup>C-Urea Breath Testing for CO Production Rates in Children; *J Pediatr Gastroenterol Nutr* 1999;29:297-301.
2. Guidance for Industry: *Helicobacter pylori*-Associated Duodenal Ulcer Disease in Adults: Developing Drugs for Treatment. October 2009. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184500.pdf>, assessed October 2011.
3. Draft Guidance for Industry and FDA Staff: Establishing the Performance Characteristics of *In Vitro* Diagnostic Devices for the Detection of *Helicobacter pylori*. September 23, 2010. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM227110.pdf>, assessed October 2011.