CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-314

Clinical Pharmacology and Biopharmaceutics Review

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-314	Submission Date(s): June 26, 2002
Brand Name	BreathID™
Generic Name	^{13}C-Urea as part of the IDkit-hp™
Reviewer	Seong H. Jang, Ph.D.
Team Leader	Barbara Davit, Ph.D.
OCPB Division	DPEIII
ORM division	DSPID
Sponsor	Oridion Medical Ltd
Relevant IND(s)	
Submission Type; Code	Resubmitted NDA; AZ
Formulation; Strength(s)	75 mg ^{13}C-Urea Tablet
Indication	Diagnosis and post treatment monitoring of Helicobacter pylori

I. BACKGROUND

On February 2, 2001, the applicant submitted an NDA for its product, 75 mg ^{13}C-Urea tablet. The application was approvable. The approvable letter was sent on November 30, 2001. A detailed description of the principle and procedure of the test, description of the drug component, description of the drug product, and clinical pharmacology can be found in the Clinical Pharmacology and Biopharmaceutics (CPB) Review by Dr. Joette Meyer, dated 11/28/01. In the approvable letter, the applicant was asked to provide additional dissolution data from three tablet batches in water using sampling time points of 5, 10, 15 and 30 minutes. In this submission, the sponsor responded to the FDA issues presented in the approvable letter of 11/30/01.

II. BIOPHARMACEUTICS

Composition

^{13}C-Urea Urea Tablet, 75 mg

Component	Function	mg /tablet	% w/w
^{13}C-Urea	Active	75.0	
[redacted]			
Total		86.0	

Citrica powder

Component	g/pouch	% w/w
Citric Acid, NF	4.0	
Aspartame, NF		
Tutti Frutti Flavor		
Total Pouch Contents Weight	4.3	

Citrica power was reformulated without the [ ] (FD&C No.6) and with Tutti Frutti flavor [ ] instead of [ ] in accordance with FDA request.

Dissolution method and specification

A detailed description of the dissolution method was provided in the previous CPB Review, dated 11/28/01.
Briefly, the method is as follows;

Apparatus:	USP apparatus 2 (paddle)
Dissolution medium:	[ ] water at 37°C
Volume:	500 ml
Paddle speed:	50 rpm

The proposed method was found acceptable to DPE3 in the previous review cycle. Dissolution data in other medium than Citrica solution are not needed because the ^{13}C-Urea tablet is dissolved before the patient consumes it.

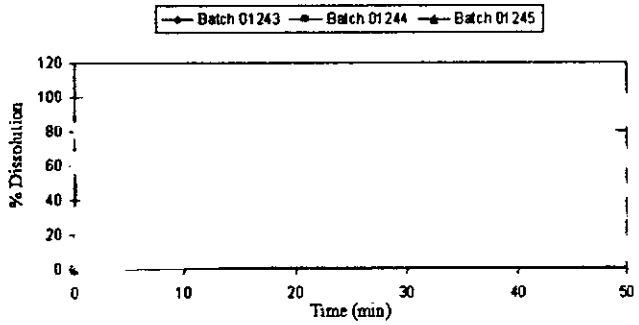
The applicant provided new dissolution data at 5, 10, 15, and 30 minutes from three validation batches, as requested by FDA. The results are summarized in the following figure and table.

Table 1 Summary of dissolution tests

Dissolution results of C^{13} Urea Tablets, 75 mg (Validation batches)			
Time (min)	Batch 01243	Batch 01244	Batch 01245
5	101 [ ]	94 [ ]	98 [ ]
10	102	103	101
15	103	104	101
30	103 [ ]	104 [ ]	101 [ ]
45	103	104	101

*: % dissolution, Mean (range)

Figure 1. Dissolution results of ^{13}C urea tablets



The applicant proposed to change the specification from not less than (NLT) [ ] (Q) at — minutes to NTL[ ] (Q) at 15 min, based on a review of the previous dissolution results for three different batches. This change to the proposed specification is acceptable.

Comment by reviewer:

According to the new dissolution data, ^{13}C-Urea tablets dissolve very rapidly, i.e., more than 94% of the substance, ranging from [ ] is dissolved within 5 min. Therefore, dissolution is not an issue for its therapeutic use.

III. RECOMMENDATION

Based on the new dissolution data submitted in this resubmitted NDA, DPE3 concludes that the applicant has presented adequate information to address the FDA issues, as recommended in the previous Approvable letter. The changes in label corresponding to FDA's recommendation are also acceptable. The proposed label is attached.

/S/

Seong H. Jang, Ph.D.
Reviewer

Clinical Pharmacology and Biopharmaceutics
HFD-590
DPEIII/OCPB

Concurrence /S/

Barbara Davit, Ph.D.
Team Leader
Clinical Pharmacology and Biopharmaceutics
HFD-590
DPEIII/OCPB

21 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

/s/

Seong Jang
11/15/02 09:59:49 AM
BIOPHARMACEUTICS

Bringing new file to DFS. I deleted old one. Thanks

Barbara Davit
11/15/02 11:10:16 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	21-314
Submission Date:	2/2/01
Drug:	^{13}C-urea as part of the IDkit-hp™
Device:	BreathID™ System
Sponsor:	Oridion Medical Ltd. Jerusalem, Israel
US Agent:	Richard Eagling
US Address:	Oridion BreathID Inc. 77 Franklin Street Boston, MA 02110
Type of Submission:	New NDA
OCPB Reviewer:	Joette M. Meyer, Pharm.D.

I. BACKGROUND

Several urea breath tests (UBTs) have been FDA approved and contain ^{13}C- or ^{14}C-urea. Pranactin was the first ^{13}C-urea diagnostic drug to be approved in 1996 as part of the Meretek UBT Kit. It contains 125 mg of ^{13}C-urea. In 2001 Meretek also obtained approval for a UBT (BreathTek) containing 75 mg of ^{13}C-urea in combination with citric acid powder. The Pylori-Check Breath Test by Alimenterics contains 100 mg of ^{13}C-urea. The Metabolic Solutions Ez-HBT Helicobacter Blood Test also uses ^{13}C-urea (125 mg), but ^{13}C is detected in the blood, as opposed to detection in the exhaled breath.

II. PRINCIPLE AND PROCEDURE OF THE TEST

The BreathID™ system is intended for use as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult humans.

The BreathID system is comprised the following components:

- 75 mg ^{13}C-urea (tablet)
- One 4.4 gram packet of Citrica powder (flavored citric acid)
- One straw
- IDcircuit – nasal cannula (sampling device)
- BreathID device – analysis and printout of results

The patient is connected to the BreathID system and the patient's $^{13}CO2/^{12}CO2$ ratio in exhaled breath is monitored before and after the test solution is ingested ratio using Molecular Correlation Spectrometry (MCS), Oridion's proprietary gas measuring technology. The test solution consists of a 75 mg tablet of ^{13}C-urea and 4.5 g of Citrica powder dissolved in 200 mL of tap water. If *H. pylori* infection is present, urease splits the urea to produce $^{13}CO2$ and ammonia (NH_3). The $^{13}CO2$ then diffuses into the bloodstream and is excreted by the lungs into exhaled air. The increased ratio of $^{13}CO2/^{12}CO2$ in the exhaled breath is measured and detected by the BreathID system. In the absence of *H. pylori* infection, the entire dose of ingested urea is absorbed in the gastrointestinal tract and appears unchanged in the urine. The BreathID device software has a predictive algorithm that continually analyzes the trend of measured results and determines if the measurements will be positive or negative. Results are displayed in real time on a computer screen and are printed after completing the test. Following the ingestion of the test solution, the eintire procedure takes 20 to 30 minutes. The system is intended for use under the supervision of trained physicians, nurses, or other health care professionals.

III. DESCRIPTION OF THE DRUG COMPONENT

The diagnostic drug component of the kit is ^{13}C enriched urea. The carbon in the drug is predominately Carbon-13, a stable, naturally occurring, non-radioactive isotope of carbon which has no known pharmacodynamic effects. The ^{13}C urea drug component is supplied as a 75mg tablet in a sealed pouch. The tablet is dissolved in a glass of water and citric acid powder before oral administration. The ^{12}C isotope is the prevalent kind in nature, accounting for approximately 99% of all carbon atoms. The applied product contains the substrate ^{13}C-urea (99% ^{13}C and 1% ^{12}C).

IV. CLINICAL PHARMACOLOGY

General

Urea is a naturally occurring substance present in many foods and in man. Urea is "generally recognized as safe" for use in food (21 CFR 184.1923). It is water-soluble and the endogenous end product of protein metabolism. It functions in the removal of ammonia from the body. The daily production of urea in humans is approximately 25 to 30 gm, depending on the protein content in the diet.

The physical and chemical properties of ^{12}C-urea and ^{13}C-urea are virtually identical. The ^{13}C-isotope of carbon represents about 1% of all carbons. Calculations show that the endogenous ^{13}C-urea pool ranges from 7 to 22 mg in a 70 kg adult. The addition of 75 mg of ^{13}C-urea, equivalent to approximately 16 mg of ^{13}C, is not considered to have any biological consequences.

Pharmacokinetics

The sponsor has not conducted pharmacokinetic studies with ^{13}C-urea. Instead, the following information on the absorption, distribution, metabolism, and elimination of urea from the human body originates from reports from the published scientific literature.

Although ^{13}C-urea is administered orally, the absorption of urea is not necessary for the drug to act as a detection substrate for *H. pylori*. Therefore, bioavailability is not meaningful. Bacteria in the lower gastrointestinal tract degrade about 25-30% of an orally administered dose prior to absorption. The remaining portion of the dose is absorbed and excreted in the urine. The volume of distribution of urea is roughly the same as total body water. The clearance and elimination half-life of urea have been reported in the literature to be about 60 mL/min for healthy male subjects and about 5 mL/min for patients with renal failure and uremia. Healthy subjects and patients with renal failure have tolerated administration of doses of isotope-labeled urea similar to the 75-mg dose of ^{13}C-urea contained in the IDkit-hp without serious adverse events.

V. BIOPHARMACEUTICS

Composition

Urea: Each soluble 75 mg tablet contains:
Active ingredients: ^{13}C-enriched urea (99%)
Excipients: [ ]

Citrica: Each 4.5 gram packet contains 4 grams citric acid, [ ] aspartame, [ ] [ ] FD&C yellow #6.

Dissolution Method and Specification

The manufacturer of the ^{13}C-urea tablets used in the pivotal clinical trial was [ ] The to-be-marketed tablet was not used in the clinical trial and will be manufactured by [ ] The only difference between the tablets is the manufacturing site. The applicant performed comparative dissolution analyses on both tablets in various media:

- Water
- Citric acid solution that mimics the Citricia solution ingested by the patient, in terms of pH (≈ 2.0) and concentration (≈ 4 gm in 200 ml).
- USP pH 4.5 buffer
- USP pH 7.6 buffer

The resulting graphs and data can be found in Appendix 1. The applicant calculcated the f2 similarity factor from profiles in each type of media. The results are shown below.

Media	F2
Water	45.8
Citric acid solution	83.7
USP pH 4.5 buffer	90.1
USP pH 7.6 buffer	59.0

Reviewer's Comment: The f2 factor should be calculated using time points before and only one point after both tablet formulations achieve — dissolution. Since at least [ ]% dissolution occurs in all instances by 5 minutes, except — tablets in water, the validity of these values is questionable. Also of note, USP pH 7.6 buffer is not one of the recommended media for dissolution mentioned in the BCS Guidance.

The applicant proposes the following method and specification.

Proposed Dissolution Method and Specification [ ]

Dosage Form	Film-coated Tablet
Strength	75 mg
Apparatus	USP Apparatus 2 (paddle)
Dissolution Medium	— Water at 37°C
Volume	500 mL*
Paddle Speed	50 rpm
Sampling Time	5, 10, and 30 minutes
Analytical Method	HPLC with UV detection —
Specification	Q= — at — minutes

*chosen instead of — mL in order to obtain the appropriate sensitivity for the HPLC method

The proposed dissolution method is acceptable. However, it is recommended that the proposed specification be tightened to Q= —, at — minutes.

BE Waiver

Upon review of the data, it appears that water and USP pH 4.5 buffer are more discriminating media than the citric acid solution or USP pH 7.6 buffer.

Due to the following observations, the requirement for an in vivo bioequivalence study is waived:

- Identical components and composition between the — (clinical formulation) and — tablets (to-be-marketed formulation)

- Identical manufacturing equipment, including make, model and working principle, between the [ ] sites
- Greater than 90% dissolution in citric acid media at 5 minutes for both the [ ] and [ ] tablets
- The ^{13}C-urea tablet is meant to be dissolved with Citrica powder in water prior to ingestion as a solution
- The Procedure section of the drug-device lable contains adequate information on dissolution of the tablet prior to ingestion
- The solution will be prepared and administered under the supervision of trained medical personnel

VI. GENERAL COMMENTS NOT TO BE SENT TO THE APPLICANT

1. Due to outstanding Chemistry issues, this drug/device will be made "Approvable", pending resolution of these issues.

VII. GENERAL COMMENTS TO BE FORWARDED TO THE APPLICANT

1. The applicant will be requested in the Approvable letter to provide additional dissolution data from three tablet batches in water using sampling time points of 5, 10, 15, and 30 minutes. These data will allow us to determine a more therapeutically relevant dissolution specification.

VIII. LABELING COMMENTS FOR THE APPLICANT

1. *Please modify the following wording in the label under "Description of the ^{13}C enriched urea Drug Component" to the following:*

[

]

2. *Add the following sentence under Warnings and Precautions.*

[ ] visible in the reconstituted ^{13}C-urea and Citrica powder solution after through mixing for 5 minutes, the solution should not be used.

IX. RECOMMENDATION

The pharmacokinetic information in the literature has been found to be acceptable to support approval of ^{13}C-urea as part of the IDkit-hp for the detection of *Helicobacter pylori* in the human stomach.

The dissolution method (USP Apparatus 2, 50 rpm, in 500 mL of water) is acceptable. However, the applicant is requested to submit additional dissolution data to set the specification prior to approval.

Please forward the general comment in Section VII and labeling comments in Sections VIII on to the applicant.

/S/

Joette M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

/S/

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader)

cc: HFD-590: /NDA 21-092
/PM/KongY
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ

Appendix 1 – Dissolution Results and Graphs

Figure 1
Comparative Dissolution of ^{13}C-urea Tables in Water
— Tablets (Lot 0311P/P2) versus — Tablets (Lot 00239)

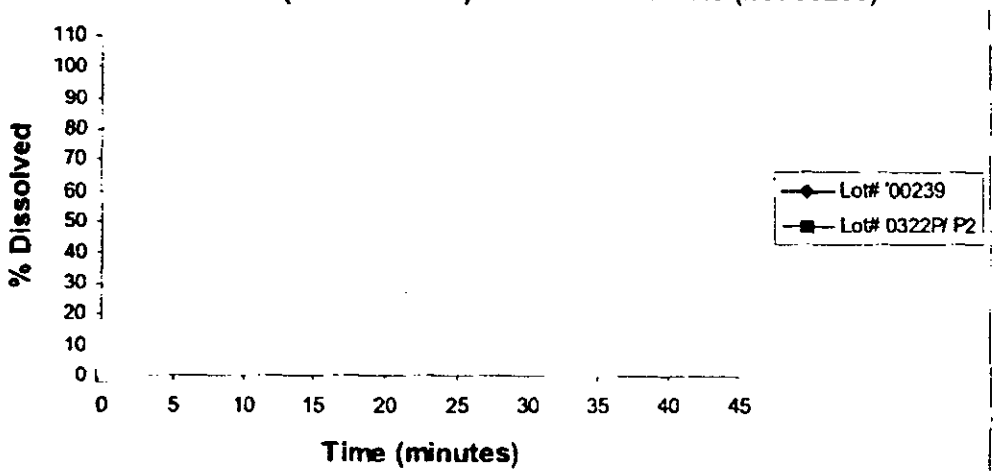


Table 1
Dissolution in Water
— Tablets (Lot 0311P/P2) versus — Tablets (Lot 00239)

	5 min		10 min		30 min		Infinity (45 min)	
Mean	100	78	101	92	101	104	101	104
%RSD	2.8	28.9	1.1	13.2	1.0	2.3	1.1	2.2
Range								

Lot 0311P/P2, Lot 00239 – n=24; [redacted] – n=12

Figure 2
Comparative Dissolution of ^{13}C-urea Tables in Citric Acid
— Tablets (Lot 0311P/P2) versus — ablets (Lot 00239)

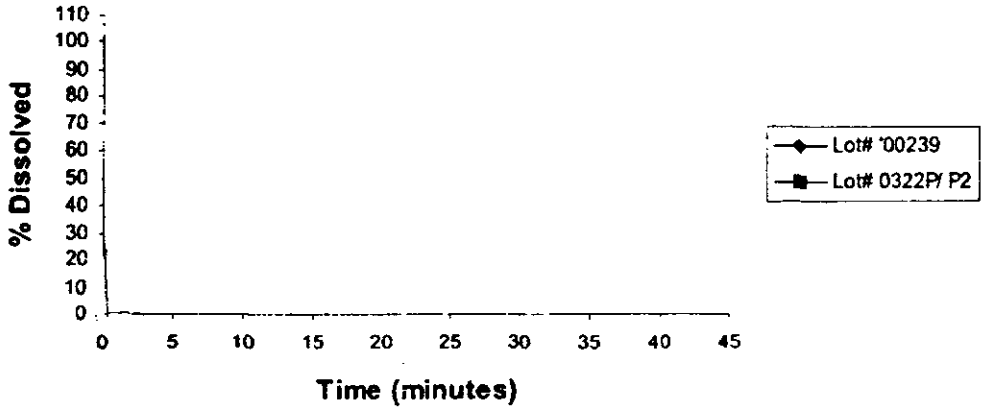


Table 2
Dissolution in Citric Acid
— Tablets (Lot 0311P/P2) versus — Tablets (Lot 00239)

	5 min		10 min		30 min		Infinity (45 min)	
Mean[a]	100	97	102	100	102	102	102	103
%RSD	4.0	16.2	1.4	9.4	0.9	0.8	1.0	0.8
Range								

[redacted] Lot 0311P/P2.
[redacted] Lot 00239
[redacted] n=24, [redacted] n=12.

Figure 3
Comparative Dissolution of ^{13}C-urea Tables in pH 4.5 Buffer
— Tablets (Lot 0311P/P2) versus — Tablets (Lot 00239)

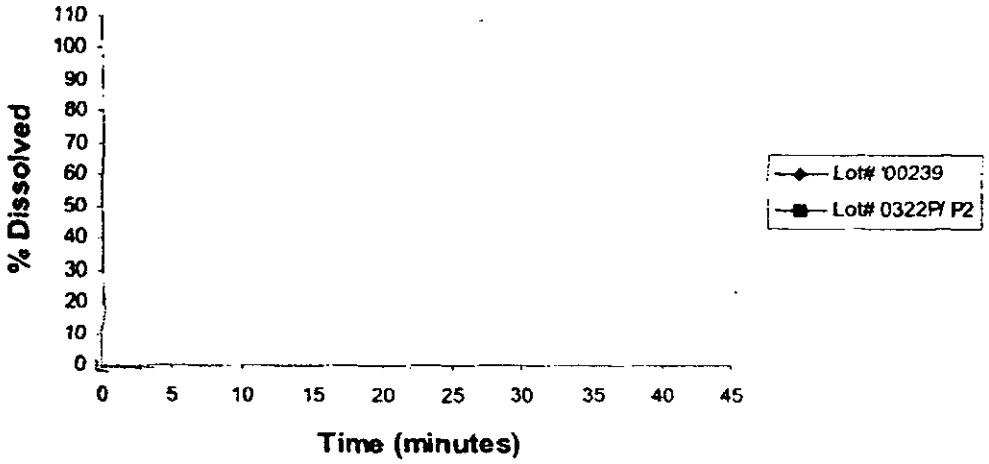


Table 3
Dissolution in pH 4.5 Buffer
— Tablets (Lot 0311P/P2) versus — Tablets (Lot 00239)

	5 min		10 min		30 min		Infinity (45 min)	
Mean[c]	99	88	100	97	100	104	99	104
%RSD	1.7	23.2	1.0	11.4	0.9	2.0	1.6	2.3
Range								

[redacted]Lot 0311P/P2.
[redacted]Lot 00239
[redacted] – n=12; [redacted] – n=12.

Figure 4
Comparative Dissolution of ^{13}C-urea Tables in pH 7.6 Buffer
— Tablets (Lot 0311P/P2) versus — Tablets (Lot 00239)

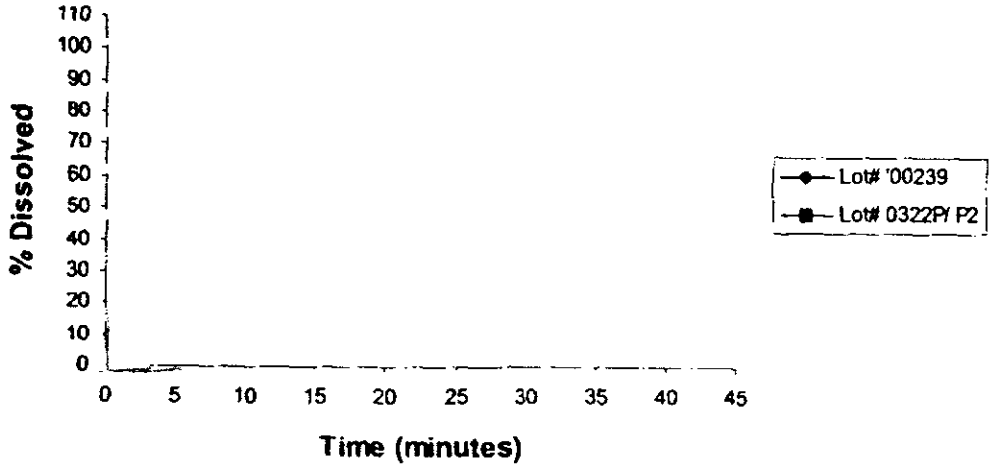


Table 4
Dissolution in pH 7.6 Buffer
— Tablets (Lot 0311P/P2) versus — Tablets (Lot 00239)

	5 min		10 min		30 min		Infinity (45 min)	
Mean[c]	99	99	101	102	101	102	101	103
%RSD	3.2	2.5	1.2	1.3	1.3	1.4	0.9	1.4
Range	[redacted]							

[a] Lot 0311P/P2.
[b] Lot 00239
[c] [redacted] n=24, [redacted] n=12.

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

/s/

Joette Meyer
11/28/01 04:24:09 PM
BIOPHARMACEUTICS

Funmilayo Ajayif
11/28/01 04:31:48 PM
BIOPHARMACEUTICS