CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-314

Pharmacology Review(s)

PHARMACOLOGY / TOXICOLOGY REVIEW AND EVALUATION

NDA#: 21-314
Serial No.: 000
Type: Original NDA Submission – Nonclinical Pharmacology and Toxicology
Date of Submission: 2/2/01

Review Division: Special Pathogen and Immunologic Drug Products
HFD-590
Reviewer: Stephen G. Hundley, Ph.D., Pharmacologist
Review Completion Date: 11/27/01

Sponsor: Oridion BreathID, Inc.
150 JFK Parkway, Suite 100
PO Box 99
Short Hills, NJ 07078

Phone Number: 973-847-5922

Drug Information

Name:	^{13}C-Urea Tablets
Product Name:	Oridion BreathID™ System
Chemical Name:	^{13}C-Urea
CAS#:	58069-82-2
Molecular Formula:	$(NH_2)_2\ ^{13}CO$
Molecular Weight:	61.06 – 61.36
Chemical Formula:	$H_2N^{13}CONH_2$

Drug Category: Diagnostic Medical Device
Related Submissions: Not Applicable

Indication: Diagnosis of *Helicobacter pylori* in the gastrointestinal tract

BACKGROUND

The proposed drug product is a diagnostic medical device designed to detect the presence of *Helicobacter pylori* in the gastrointestinal tract. The patient will orally take a solution containing 75 mg of ^{13}C-urea (dissolved ^{13}C-urea tablet). Expired air samples will be taken after drinking the solution and assayed for the ratio of $^{13}CO_2$ to CO_2. The scientific rationale is based upon the conversion by *H. pylori* of urea to CO_2 and NH_2 in the stomach via urease enzyme activity. If *H. pylori* is not present in the stomach the conversion of orally administered urea occurs only to a minor degree. A substantial amount of the $^{13}CO_2$ formed from ^{13}C-urea is absorbed from the stomach into the blood stream and expired in the breath and in turn can be measured by mass spectrometry.

There is no therapeutic activity associated with ^{13}C-urea in this administration regimen. Oral administration of 75 mg ^{13}C-urea has no pharmacologic or toxicologic activity. The stable isotope ,^{13}C, has no toxicologic properties and urea is a normal biochemical constituent in mammalian systems and is in much higher levels in humans than presented by the 75 mg oral dose. The sponsor cites and provides pertinent literature to this effect in the submission. This is an abbreviated Pharmacology/Toxicology Review of an NDA due to the absence of any pharmacological or toxicological effects resulting from intake of urea in quantities several fold lower than endogenous levels in humans.

EVALUATION

There are no pharmacology/toxicology issues presented in this submission and the indication is reasonably safe to pursue.

/S/

Stephen G. Hundley, Ph.D.

Concurrences:
HFD-590 / R.Albrecht / Acting DDir
HFD-590 / K. Hastings / TL
Disk:
HFD-590 / K. Hastings

cc:
HFD-590 / Original NDA
HFD-590 / Division File
HFD-345
HFD-590/ PM / L. Chan
HFD-590/ PM/ Y. Kong
HFD-590 / Biopharm / J. Meyer
HFD-590 / Pharm / S. Hundley
HFD-590 / Micro
HFD-590 / Chem/ M. Seggel
HFD-590 / Stat / K. Higgins

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

/s/

Steve Hundley
11/28/01 10:42:28 AM
PHARMACOLOGIST

Kenneth Hastings
12/14/01 07:29:02 AM
PHARMACOLOGIST

Renata Albrecht
12/14/01 08:26:30 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): CDRH/ODE/DCLD **Bacteriology Devices Branch, HFZ-**
)
. reddie Poole, Supervisory Biologist
(301)594-2096

FROM: CDER/OND/ODEIV**Division of Special Pathogen and Immunologic Drug Products, HFD-590**
Joette Meyer, Pharm.D., Clinical Reviewer
Mark Seggel, Ph.D., Chemistry Reviewer
Yoon Kong, Regulatory Project Manager
cc: Rigoberto Roca, M.D., Clinical Team Leader
Norman Schmuff, Ph.D.- Chemistry Team Leader

DATE: September 23, 2002	IND NO.	NDA NO. **21-314**	TYPE OF DOCUMENT- Resubmission Class Type II	DATE OF DOCUMENT (Stamp Date) **June 26, 2002**
NAME OF DRUG: **13 C Urea tablet and Citrica powder for Oridion BreathID**	PRIORITY CONSIDERATION: **6 months**		CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: **October 25, 2002**

NAME OF FIRM: Oridion Medical Ltd.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please provide validation for the Isotope Ratio Mass Spectrometry (IRMS) procedure, (currently not approved by FDA) which was used in the Shirin study ("Clinical Study on the Effect of Proton Pump Inhibitors on the Oridion 13C Urea BreathID Test") in Israel. [

Background: On November 30, 2001, the sponsor was issued an "Approvable" letter for their NDA 21-314 application.
[ ] On July 26, 2001, 510k application (K011668) was approved. We are aware of the Hadassan study (submitted in the original NDA), in addition to the Shirin study where the IRMS was utilized. Please, if available, provide us with a copy of your initial review of this study in which the BreathID was compared to the IRMS. Attached to this consult, we are sending a copy of the volumes 11 [ ] for your review. Also, attached are the following: copy of the "Approvable " letter issued on November 30, 2001from our division and the most recent revised Package Insert (PI) submitted. If you have any questions or concerns, please contact Joette Meyer @ (301) 827-2429 or Yoon Kong @ (301) 827-2195.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ■ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Yoon Kong
9/23/02 04:08:38 PM
Consult package sent via internal mail to CDRH.

FDA/CDRH/OIVD

Consultation Memo

To: Freddie Poole
Deputy Director
Division of Microbiology Devices, OIVD

From: Wendy R. Sanhai, Ph.D.
Scientific Reviewer
Chemistry and Toxicology Branch/DCLD/ODE [Click **here** and type name]

CC: Jean Cooper, D.V.M.

Deputy Director

Division of Chemistry and Toxicology Devices, OIVD

Date: January 6, 2003

Re: **Validation for the Isotope Ratio Mass Spectrometry (IRMS)**
[510(k)] K003950: Oridion Medical Ltd. Breath Test System
Related to NDA: 21-314

Background

Oridion Diagnostics, Ltd. submitted this pre-market notification to obtain a substantial equivalent determination for the BreathID™ Test System. This test system is a combination *in-vitro* diagnostic device (K003950) and *in-vivo* drug (NDA: 21-314). Our Office of In-Vitro Diagnostics and Safety (OIVD) was asked to provide validation for the Isotope Ratio Mass Spectrometry (IRMS) procedure (currently not approved by the FDA) which was used in the Shirin Study (Clinical Study on the Effect of Proton Pump Inhibitors on the Oridion ^{13}C Breath ID™ Test) as supportive data for their submission of NDA 21-314 that is linked to said 510 (k) submission.

In an effort to provide a time-line of events for this case, the following memos regarding this case have been attached:
(1) Review Memo dated January 16, 2001, prepared and submitted by Freddie Poole;
(2) Telephone Memo dated March 8, 2001, between representatives at Oridion Medical and Freddie Poole and Woody Dubois;
(3) Review Memo dated July 2, 2001, prepared and submitted by Freddie Poole.

Since this memo focuses on the validation of the IRMS procedure, details contained in the aforementioned three memos will not be discussed further. Please refer to the attached memos for information regarding previous reviews for this case.

Predicate device

The Meretek Diagnostic UBT® Breath Test.

Intended Use

The Oridion BreathID™ Test System is intended for use in the (non-invasive) 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. The test may be used for monitoring treatment if used at least four (4) weeks following completion of therapy. For these purposes, the system utilizes Molecular Correlation Spectrometry (MCS) for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples. The test is intended for use by trained health care professionals, and should be administered under a physician's supervision.

Principle of the Oridion BreathID™ Test

In the Oridion (non-radioactive) ^{13}C BreathID™ Test, 75 mg of dissolved ^{13}C-Urea and Citrica powder (drug component) are dissolved in 200 ml of water and ingested by the patient. In the presence of the urease enzyme, associated with gastric *H. pylori* in infected patients, ^{13}C-Urea is decomposed to $^{13}CO_2$ and NH_4 according to the following equation:

$$2\ ^{13}\text{C-Urea} + 2H_2O \xrightarrow[\text{Urease}]{\textit{H. pylori}} 2\ ^{13}CO_2 + 2NH_3$$

The $^{13}CO_2$ is absorbed into the blood, then exhaled in the breath. A baseline sample of exhaled breath is collected through a nasal cannula and also analyzed. The patient continues to breath normally after consumption of the drug component and the Oridion ^{13}C BreathID™ Test System records the changes in the $^{13}CO_2/^{12}CO_2$ ratio. The instrument ends the measurement automatically when there is sufficient data to determine if the results are positive (for *H. pylori)* or negative.

Review Summary for Validation of the IRMS Procedure

As all of these may impact the results obtained, the following supplementary information was requested from the applicant:

- A brief explanation of the methodology (including the principles of this test, how the instrument functions, controls runs etc.) and reason/s why the investigators used mass spec. for measuring the ^{13}C concentration;
- Information on how the instrument was calibrated;
- Information on how the samples were collected and shipped: time delay between collection and actual runs on the mass spect., conditions for shipment; whether on ice, in plastic bags; measures taken to ensure that amount of sample collected corresponded to amount of sample actually tested i.e. no loss of sample during shipment?
- A protocol giving details for testing.

The aforementioned information was submitted and subsequently reviewed. The questions regarding the methodology, calibration, sample-transport and handling and protocol for the IRMS method were satisfactorily addressed.

- In 49 out of the 50 cases described in the submitted data, there was strong correlation between the Oridion ^{13}C Breath ID™ Test and the Isotope Ratio Mass Spectrometry (IRMS) methods:

- McNemar analysis, which analyzed the comparative performance, revealed no significant difference between these two methods.

- Samples were collected at one site and analyzed at another site (approximately 5 miles apart). From the protocol submitted, there is little concern regarding sample-identification and collection procedures. Samples were stored at room temperature in sealed in vacutainers for analyzed 0-68 days after collection. While there are no obvious concerns about sample integrity over this

extended period, it may be advisable to perform a study to address any potential problems regarding this time delay between sample collection and analysis.

Conclusion

Although the IRMS procedure, which was used in that Shirin Study is currently not approved by the FDA, the comparative data for the FDA-cleared Oridion ^{13}C Breath ID™ Test and the IRMS method demonstrates good correlation. There were no significant differences between these two methods.

Please feel free to contact me at 301-594-1243 X 122 with additional questions regarding this IRMS validation.

/S/

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Wendy R. Sanhai, Ph.D. Date

Consulting Reviewer

FDA/CDRH/OIVD