CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-314

Administrative/Correspondence Reviews

13.0 Patent Information

TIME SENSITIVE

PATENT INFORMATION
[21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.53]
for
NDA # 21-314

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Breath ID
- Active Ingredient(s): ^{13}C-urea
- Strength(s): 75 mg
- Dosage Form: tablet
- Approval Date:

In accordance with 21 U.S.C. § 355(b)(1) and 21 C.F.R. § 314.53, the required information for each individual patent issued by the United States Patent and Trademark Office that claims ^{13}C-urea or an approved use for ^{13}C-urea is provided on the following page.

U.S. Patent Number: 6,067,989
Expiration Date: May 30, 2020
Type of Patent--Indicate all that apply:

Drug Substance(Active Ingredient) ___Y _x_N

Drug Product(Composition/Formulation) ___Y _x_N

Method of Use _x_Y ___N

The approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Breath test for the diagnosis of *Helicobacter pylori* in the gastrointestinal tract.

Name of Patent Owner: Oridion Medical 1987, Ltd., Jerusalem, Israel

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

Oridion BreathID, Inc.
150 JFK Parkway, Suite 100
Short Hills, New Jersey 07078

Original Declaration

The undersigned declares that the above stated United States Patent Number 6067989 covers the composition, formulation and/or method of use of ^{13}C-urea. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act).

1 Feb 2001

Sanford Brown — Date

Regulatory Affairs Manager

Telephone Number : +9722-589-9115

14.0 Patent Certification

The patent certification is not applicable to this submission.

Appears This Way
On Original

EXCLUSIVITY SUMMARY for NDA # 21-314 SUPPL #

Trade Name IDkit-Hp™

Generic Name ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0g for the Oridion BreathID® Breath Test System.

Applicant Name Oridion Medical 1987 Ltd. HFD- 590

Approval Date December 17, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_ __/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-586 Meretek UBT with Pranactin (125 mg of 13C-urea)

NDA # 20-586/S-002 BreathTek UBT with Pranactin-Citric (75 mg of 13C-urea)

NDA # 21-092 Ez-HBT Helicobacter blood test with Helicosol (125 mg of 13C-urea)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to

the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 5266

Investigation #2, Study # Dr. Haim Shirin Clinical Trial in Israel entitled: "Effect of Proton Pump Inhibitors on the Continuous Real Time ^{13}C-urea Breath Test." Principal Investigator: Haim Shirin, MD, Wolfson Medical Center, Israel

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 5266

Investigation # 2 , Study # Clinical Trial in Israel entitled: "Effect of Proton Pump Inhibitors on the Continuous Real Time ^{13}C-urea Breath Test." Principal Investigator: Haim Shirin, MD, Wolfson Medical Center, Israel

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # __YES /_ __/ ! NO /_ __/ Explain:

Investigation #2

IND # _____ /___/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /_ X__/ Explain _____ ! NO /___/ Explain _____

Studies were conducted to support 510(K) K011668.

Investigation #2

YES /_X__/ Explain _____ ! NO /___/ Explain _____

Studies were conducted to support 510(K) K011668.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

Susan Peacock, M.S.
Signature of Preparer Date
Title: Regulatory Project Manager

Renata Albrecht, M.D.
Signature of Office or Division Director Date

cc:
Archival NDA
HFD-590/Division File
HFD-590/Susan Peacock
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Renata Albrecht
3/26/03 02:45:55 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # : 21-314 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: 26 June 2002 **Action Date:** 17 December 2002 **HFD** 590

Trade and generic names/dosage form: IDkit:Hp™ containing ^{13}C-Urea (^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0 g for the Oridion BreathID® Breath Test System.

Applicant: Oridion Medical 1987 Ltd. **Therapeutic Class:**

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: The Oridion BreathID system containing 75 mg 13C-urea is to be used as an aid for initial diagnosis and post-treatment monitoring of *Helicobacter pylori* infection

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** X **Partial Waiver** X **Deferred** ____ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg** ____	**mo.** ____	**yr.** 0	**Tanner Stage** ____
Max ____	**kg** ____	**mo.** ____	**yr.** 2	**Tanner Stage** ____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.** >2	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.** 16	**Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 12/31/07

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-314
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Ellen Frank
12/27/02 03:42:35 PM

16.0 Debarment Certification

Oridion Medical 1987 Ltd. hereby certifies that it did not and will not use in any capacity the services of any person debarred pursuant to the Federal Food, Drug, and Cosmetic Act 306(k)(1) in connection with this application.

Sanford Brown — 16 Jan 2001

Sanford Brown
Date

Regulatory Affairs Manager

Oridion Medical 1987 Ltd.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 11 2001

Sanford Brown
Regulatory Affairs Manager
Oridion Medical 1987 Ltd.
P.O. Box 45025
Jerusalem 91450
Israel

RE: Oridion Medical 1987 Ltd., New Drug Application 21-314
Small Business Waiver Request 2001.005

Dear Mr. Brown:

This letter responds to your letter received September 25, 2000, requesting a waiver of the human drug application fee for a new drug application (NDA) 21-314 under the small business waiver provision of section 736d(1)(E)[1] of the Federal Food, Drug, and Cosmetic Act (the Act)[2] (Waiver Request 2001.005). For the reasons described below, the Food and Drug Administration (FDA) grants the request from Oridion Medical 1987 Ltd. (Oridion) for a small business waiver of the application fee.

According to your waiver request, Oridion presently employs fewer than 500 individuals including your affiliates: Oridion Medical, Inc., Oridion BreathID, Inc., Oridion Spain, S.L., and Oridion Systems Ltd. You also state that the NDA for the drug component of the BreathID System is the first human drug application Oridion and its affiliates will submit to the Agency for review.

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate[3] submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets two criteria: (1) a business must employ fewer than 500 persons, including employees of its affiliates, and, (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

---

[1]21 U.S.C. 379h(d)(1)(E).

[2]Sections 735 and 736 of the Act (21 U.S.C. 379g and 379h).

[3]"The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly - (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

Oridion Medical Ltd.
Waiver Request # 2001.005

FDA's decision to grant a small business waiver to Oridion is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its by letter dated November 27, 2000, that Oridion has fewer than 500 employees, including those of its affiliates: Oridion Systems Ltd., Irad Technologies Ltd., Oridion Medical Inc., Oridion BreathID Inc., and Oridion Spain S.L. Second, according to FDA records, the marketing application for BreathID Test System, NDA 21-314, will be the first human drug application, within the meaning of the Act, to be submitted to FDA by Oridion or its affiliates. Consequently, your request for a small business waiver of the application fee for BreathID Test System, NDA 21-314, is granted.

FDA records show that NDA 21-314 has not been submitted yet. Please include a copy of this letter with your NDA when it is submitted. If FDA refuses to file the application or Oridion withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Oridion should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether Oridion continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

PLICANT'S NAME AND ADDRESS

)ridion Medical 1987, Ltd.
/Ha Marpe
).O. Box 45025
)1450 Jerusalem, Israel

3. PRODUCT NAME
Urea-13C (Carbon-13 Urea)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. Yes

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

ELEPHONE NUMBER *(Include Area Code)*
011)972-2-589-5115

SER FEE I.D. NUMBER
Not Required

6. LICENSE NUMBER / NDA NUMBER
NDA 021314

THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

AS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☒ YES ☐ NO
(See reverse side if answered YES)

l completed form must be signed and accompany each new drug or biologic product application and each new pplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

IATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Manager Reg Affairs	23 January

M Fo... ...97 (5/98)

Financial Information (Section 18)

18.2 Letter Granting Waiver of User Fee

A letter, dated January 11, 2001, granting Oridion Medical 1987, Ltd a waiver of the human drug application fee for their new drug application (NDA 21-314) under the small business provision of 21 U.S.C. Section 736d(I)(E) of the Federal Food, Drug and Cosmetic Act can be found on the following pages.

Appears This Way
On Original

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-314	Efficacy Supplement Type SE-	Supplement Number
Drug: IDkit:Hp™ containing ^{13}C-Urea·(^{13}C-urea tablet for oral solution) 75 mg, and Citrica (citric acid powder for oral solution) 4.0 g for the Oridion BreathID® Breath Test System.	Applicant: Oridion Medical 1987 Ltd.	
RPM: Susan Peacock, M.S., M(ASCP)	HFD-590	Phone # 301-827-2127
Application Type: () 505(b)(1) (X) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Type 3- New Formulation
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	12-26-02
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid N/A
• User Fee waiver	(X) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other N/A
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted ***Emailed sponsor on March 27, 2003, requesting submission of patent certification.**	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of	( ) Verified N/A

notice).	
❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Approvable, 11/30/2001 Approval, 12/17/2002
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable Approval email
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X DDMAC 12-6-01 OPDRA 10-15-01
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	See Chemistry Review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	X

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	12-18-01, 3-26-03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	4-11-01
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Clinical Review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	12-18-01 (See clinical)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	11-28-01
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	See Clinical Review
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	1-29-02, 12-17-02
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	See chemistry review (1-29-02)
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report) **(See chemistry review, part VII)**	Date completed: **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation **(See chemistry review)**	( ) Completed **(X)** Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	12-14-01
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

7/2/02

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/s/

Ellen Molinaro
10/27/03 04:34:47 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-314 /SE_____ - _____

Drug BreathID System (device/drug)- Applicant Oridion Medical 1987 Ltd.
Drug Component : Idkit-H.p.

RPM Yoon Kong, Pharm.D., RPM Phone (301) 827-2195

☐505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: ■ S ☐P

Pivotal IND(s) : 510 k (K011668) cleared in CDRH on 7-9-01

Application classifications:
Chem Class 1S
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary 12-02-01
Secondary 2-02-01

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☐ User Fee Paid
  ■ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter..... ☐AP ■ AE ☐NA
- CDRH Action and Designation Letters X
- DDMAC Consult Review X
- Labeling & Labels
  - FDA revised labeling and reviews..... X
  - Original proposed labeling (package insert, patient package insert) X
  - Other labeling in class (most recent 3) or class labeling..... Meretek (N 20-586)
  - Has DDMAC reviewed the labeling? ..... ■ Yes (include review) ☐ No
  - Immediate container and carton labels X
  - Nomenclature review X
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.

Exception for review (Center Director's memo)..... N/A
OC Clearance for approval..... N/A

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter
- Post-marketing Commitments N/A
  - Agency request for Phase 4 Commitments..... N/A
  - Copy of Applicant's commitments ..... N/A
- Was Press Office notified of action (for approval action only)?..... ☐ Yes ☐ No
  - Copy of Press Release or Talk Paper..... N/A
- Patent
  - Information [505(b)(1)] ..... 505(b) - X
  - Patent Certification [505(b)(2)]..... _____
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... _____
- Exclusivity Summary ..... N/A (Approvable)
- Debarment Statement X
- Financial Disclosure
  - No disclosable information ..... _____
  - Disclosable information – indicate where review is located ..... See MO Review
- Correspondence/Memoranda/Faxes X
- Minutes of Meetings X
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting _____
  - Date of pre-AP Safety Conference N/A
- Advisory Committee Meeting ..... N/A
  - Date of Meeting ..... N/A
  - Questions considered by the committee ..... N/A
  - Minutes or 48-hour alert or pertinent section of transcript ..... N/A
- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... _____
- Clinical review(s) and memoranda ..... X (Joint Clin/Stat Review)
- Safety Update review(s) ..... See Medical Review
- Pediatric Information
  - ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ■ Deferred
  - Pediatric Page..... _____
  - ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable
- Statistical review(s) and memoranda ..... X (Joint Clin/Stat Review)
- Biopharmaceutical review(s) and memoranda..... X
- Abuse Liability review(s) ..... N/A
  - Recommendation for scheduling ..... N/A
- Microbiology (efficacy) review(s) and memoranda ..... N/A
- DSI Audits ..... See MO TL Memo
  - ☐Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda X
- Statistics review(s) and memoranda regarding dissolution and/or stability X
- DMF review(s) X
- Environmental Assessment review/FONSI/Categorical exemption X
- Micro (validation of sterilization) review(s) and memoranda ..... N/A
- Facilities Inspection (include EES report)
  - Date completed _____ ..... ■ Acceptable ☐ Not Acceptable
- Methods Validation ..... ☐ Completed ■ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda ..... N/A
- Memo from DSI regarding GLP inspection (if any) ..... N/A
- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

4 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

11-6-01

MEMORANDUM OF TELECON

DATE: November 26, 2002

APPLICATION NUMBER: NDA 21-314, IDkit-hp™ (13 C Urea) 75 mg tablet

BETWEEN:

Name: Sandy Brown, RA Director
Edna Wellner, QA Director
Yacov Bubis, COO
Daniel Katzman, Business Devlopment
[ ] Consultant

Phone: +972-2-589-9115

Representing: Oridion Medical 1987 Ltd.

AND

Name: Susan Peacock, Regulatory Project Manager
Rigoberto Roca, Clinical Team Leader
Joette Meyer, Clinical Reviewer
Mark Seggel, Chemistry Reviewer
Division of Special Pathogen and Immunologic Drug Products, HFD-590

SUBJECT: Discuss FDA version of PI, CMC questions, and [ ]

1) Any further CMC questions?

FDA Response: No

2) Does FDA agree to a [ ] expiry date?

FDA Response:

- [ ] *expiry date for the Urea is acceptable. For the citrica, a* [ ] *expiry is acceptable.*
- *The following storage statement should be included in section V,* ***Shelf life and Storage*** *section: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled RoomTemperature].*

3) Discussion of Nov. 21 FDA version of PI.

Oridion accepted all of our proposed changes in the label mailed to them on November 21, 2002.

4) FDA's position on the [ ] What does Oridion need for a label change?

FDA Response:

- [ ]
- [ ]
- [ ]

5) What else does Oridion need to address? Final packaging?

FDA Response: The Review Team asked for Oridion to submit revised labeling, PI, and packaging. Oridion agreed to send these items.

/S/

Susan Peacock
Regulatory Project Manager

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/s/

Rigoberto Roca

12/3/02 03:41:49 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: September 10, 2002

To: Richard Eagling	**From:** Yoon J. Kong
Company: Oridion Medical 1987 Ltd.	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (617) 482-0808	**Fax number:** (301) 827-2475
Phone number: (617) 306-4759	**Phone number:** (301) 827-2127

Subject: NDA 21-314

Total no. of pages including cover: 2

Comments:

Document to be mailed: • YES ☑ NO

Date: September 10, 2002

To: Richard Eagling, Ph.D.
General Manager
Oridion BreathID, Inc.
21 Highland Circle
Needham, MA 02494

From: Yoon Kong, Pharm.D.
Regulatory Project Manager, HFD-590

Through: Mark Seggel, Ph.D., Chemistry Reviewer

Subject: 13 C Urea tablet and Citrica- [redacted]

Dear Dr. Eagling:

Please refer to your resubmission of your NDA application 21-314 dated June 27, 2002, receipt dated June 26, 2002. We have the following queries to be addressed.

- The product described in your NDA resubmission contains [redacted] "Tutti Frutti Flavour [redacted]" and not [redacted] " in the reformulated Citrica. During the January 22, 2002, meeting, you had indicated that the [redacted] would be used. Please explain this change.

- Also, please provide an update of the Citrica stability study.

Please contact me at (301) 827-2127, if you have any questions regarding this facsimile transmission.

/S/

Yoon Kong, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Yoon Kong
9/11/02 10:21:45 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: August 15, 2002

To: Richard Eagling	**From:** Yoon J. Kong
Company: Oridion Medical 1987 Ltd.	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (781) 453-2722	**Fax number:** (301) 827-2475
Phone number: (781) 453-0500	**Phone number:** (301) 827-2127

Subject: NDA 21-314

Total no. of pages including cover: 3

Comments: Information Request

Document to be mailed: ☐ YES ☑ NO

Date: August 13, 2002

To: Richard Eagling, Ph.D.
General Manager
Oridion BreathID, Inc.
21 Highland Circle
Needham, MA 02494

From: Yoon Kong, Pharm.D.
Regulatory Project Manager, HFD-590

Through: Mark Seggel, Ph.D., Chemistry Reviewer
Norman Schmuff, Ph.D., Chemistry Team Leader
Joette Meyer, Pharm.D., Clinical Reviewer
Rigoberto Roca, M.D., Clinical Team Leader

Subject: 13 C Urea tablet and Citrica- [illegible] 3

Dear Dr. Eagling:

Please refer to your resubmission of your NDA application 21-314 dated June 27, 2002, receipt dated June 26, 2002.

Upon initial review your resubmission, we have the following information requests.

1. Please provide the dissolution results for the individual tablets tested from the three validation batches (i.e., 01243, 01244, 01245), as the resubmission only contains summary data (Section 6.3).

2. Please provide original patient records on the 53 patients with biopsy specimens taken from both the antrum and corpus enrolled in the pivotal Boston clinical study, including the endoscopy procedure note as well as laboratory reports for each patient.

3. Please provide the original raw data with a complete (i.e., full length) study report for the Shirin study (D005728) including information on medication(s), dates of patient visits, and results of the BreathID and IRMS testing (pre- and post-treatment).

   Also, please clarify the study design and treatment that each patient received. In the protocol, treatment with omeprazole or ranitidine is described. Were patients randomized to medication? In the data summary table it appears that there were more than two medications utilized. Please explain. If the study design was changed, was the protocol amended? *Please submit all protocol amendments.*

4. Please provide the validation report, including raw data, for the pre- and post-testing by Mass Spectrometer performed at the Gastro Institute in Beilinson Hospital.

5. Please provide us with 5 samples each of the 13C Urea tablets and Citrica powder with the appropriate packaging information.

Please contact me at (301) 827-2127, if you have any questions regarding this facsimile transmission.

/S/

Yoon Kong, Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Yoon Kong
8/15/02 12:47:00 PM
CSO
Faxed to sponsor on 8-15-02.

Yoon Kong
8/15/02 12:49:36 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: May 28, 2002

To: Richard Eagling	**From:** Yoon J. Kong
Company: Oridion Medical 1987 Ltd.	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (781) 453-2722	**Fax number:** (301) 827-2475
Phone number: (781) 453-0500	**Phone number:** (301) 827-2127

Subject: NDA 21-314

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

Date: May 24, 2002

To: Richard Eagling, Ph.D.
General Manager
Oridion BreathID, Inc.
21 Highland Circle
Needham, MA 02494

From: Yoon Kong, Pharm.D.
Regulatory Project Manager, HFD-590

Through: Mark Seggel, Ph.D., Chemistry Reviewer
Norman Schmuff, Ph.D., Chemistry Team Leader
Joette Meyer, Pharm.D., Clinical/Biopharmaceutics Reviewer
Barbara Davit, Ph.D., Biopharmaceutics Team Leader
Rigoberto Roca, M.D., Clinical Team Leader

Subject: Citrica- [ ]

Dear Dr. Eagling:

Please refer to the approvable letter issued on November 30, 2001, for [ ]

We have the following comments and recommendations regarding your product labeling, packaging and analytical procedures.

Labeling

Please make the following revisions to your current labeling.

- [ ]
- [ ]
- [ ]
- The storage statement should be consistent throughout the labeling and should include degrees Celsius and degrees Fahrenheit. The actual storage statement will depend on demonstration of adequate stability.
- [ ]

Analytical Procedures

- [ ]

Tablet Packaging

- Please note that during validation of the analytical methods at a FDA laboratory, the analyst observed that three foil pouches out of [ ] Please suggest corrective action.

Please include this information as part of your complete response to the November 30, 2001, approvable letter for NDA 21-314.

In addition, please refer to Sandy Brown's e-mail to Mark Seggel on May 14, 2002, regarding your proposal for a specification change of the ^{13}C Urea tablet dissolution to NLT [ ] (Q) at [ ] minutes. This proposal seems reasonable to us at this time. As Sandy Brown indicated in this e-mail, specifications for dissolution of the ^{13}C Urea tablet should be updated as new data becomes available to you.

If you have any questions, you can contact me at (301) 827-2127.

Yoon Kong, Pharm.D.
Project Manager
Division of Special Pathogen and Immunologic Drug Products

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/s/

Yoon Kong
5/28/02 10:52:51 AM
CSO
Faxed to sponsor on May 28, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 16, 2002

To: Richard Eagling	**From:** Yoon J. Kong
Company: Oridion Medical 1987 Ltd.	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (617) 482-0808	**Fax number:** (301) 827-2475
Phone number: (617) 306-4759	**Phone number:** (301) 827-2127

Subject: NDA 21-314

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-314

Oridion Medical 1987 Ltd.
Attention: Dr. Richard Eagling
General Manager
77 Franklin Street
Boston, MA 02110

Dear Dr. Eagling:

Please refer to the approvable letter issued on November 30, 2001, for BreathID System, and to your submission dated December 6, 2001.

We have reviewed your submission dated December 6, 2001, which requests clarification on the deficiencies cited in our approvable letter issued on November 30, 2001. We have the following points of clarification (please note that the numbers correspond to the numbers in your December 6, 2001, submission):

Deficiency 1:

- The objective of our October 31, 2001, request was to obtain all available information regarding the quality of the dye in order to allow us to fully evaluate the suitability of the material for use in this product.

  The requirements that FD&C Yellow #6 used in drugs or foods in the U.S. must conform in identity and specification to 21 CFR 74.706(a)(1) and (b), and must be certified in accordance with 21 CFR 80, are not new. Based on the information provided in the November 6, 2001 amendment, we cannot conclude that the material meets these requirements or is suitable for the intended use, since some listed tests are omitted, and there is no commitment to certify each batch as required by 21 CFR 74.706 (e). As noted in the November 30, 2001 Approvable Letter, several options are available.

Deficiency 2:

- In your December 6, 2001 meeting request, you indicate that you have a list of ingredients used to manufacture the flavor. However, it is unclear why regulatory references are not available for each component despite the assertion that "All ingredients in this product are in accordance with the American list of flavoring materials GRAS, FEMA and the FCC III." Are specifications for the components available from the supplier? As noted in the November 31, 2001 Approvable Letter, this information could be submitted in a Drug Master File.

Deficiency 3:

- The in-process controls for the Citrica packaging operation should certainly include package integrity testing. [

Deficiency 5:

- The ICH Q1A and Q1A(R) guidances state that there should be a direct link between the label storage statement and the demonstrated stability of the drug product. Please propose additional stability studies to support storage at the intended conditions. If the product is not stable — in the proposed packaging, it cannot be labeled for storage at that temperature.

Deficiency 6:

- The mean percent dissolved for the —tablets at —minutes is — however the range of the individual tablets tested is from [ ] We are interested in setting a dissolution specification of not less than —. at the time point selected. At —minutes the dissolution of all tablets is [ ] No intermediate timepoint was tested. Therefore, please repeat the dissolution testing for three batches of the tablets manufactured by — using time points of 5, 10, 15, and 30 minutes

If you have any questions, call Yoon J. Kong, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

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/s/

Yoon Kong
1/16/02 01:49:37 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 8, 2001

To: Dr. Richard Eagling	**From:** Ellen C. Frank for Yoon J. Kong
Company: Oridion Medical 1987 Ltd.	Division of Special Pathogen and Immunologic Drug Products
Fax number: (617) 482-0808	**Fax number:** (301) 827-2475
Phone number: (617) 482-4200	**Phone number:** (301) 827-2127

Subject: Requests for additional information

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-314

Oridion Medical 1987 Ltd.
C/o Dr. Richard Eagling
Oridion Medical Inc.
77 Franklin St.
Boston, MA 02110

Dear Dr. Eagling:

Please refer to your February 2, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IDkit: H.p.™ (^{13}C urea).

We also refer to your submission dated July 8, 2001 and our telephone conversation of November 7, 2001.

We are reviewing the package insert and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please clarify what instructions, if any, the patients were given regarding food prior to administration of the BreathID test. Were there any restrictions placed on timing of food in relation to the test?

2. We have been unable to match the date of *H. pylori* testing with the date of the patient's last PPI/H2 dose. Please provide the following pre-therapy and post-therapy data for each patient in Study 5266 electronically:

   a. date of last PPI/H2 dose prior to *H. pylori* testing,
   b. date of histology test,
   c. date of CLOtest,
   d. date of Meretek test (for post-therapy only), and
   e. date of BreathID test.

   Please sort the lists by subject number.

If you have any questions, call Yoon J. Kong, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Frank
11/8/01 10:10:37 AM
CSO
NDA 21-314

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-314

8/21/02

Oridion BreathID, Inc.
Attention: Richard Eagling
General Manager
21 Highland Circle
Needham, MA 02494

Dear Dr. Eagling:

We acknowledge receipt on June 26, 2002, of your June 27, 2002 (sic), resubmission to your new drug application for [ ] 13C Urea tablet and Citrica powder. Please note that we have administratively designated the letter date of your resubmission to June 26, 2002.

We consider this a complete, class 2 response to our November 30, 2001, action letter. Therefore, the user fee goal date is December 26, 2002.

If you have any questions, call Yoon Kong, Pharm.D, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/S/

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Frank
8/21/02 03:40:03 PM
NDA 21-314

FROM SPONSOR

MINUTES OF AUGUST 17, 2000 MEETING (9:30 to 11:30 am)

ORIDION MEDICAL, LTD. WITH CDER DIVISION OF SPECIAL PATHOGENIC AND IMMUNOLOGIC DRUG PRODUCTS AND CDRH – DCLD – MICROBIOLOGY BRANCH

LIST OF ATTENDEES

FDA

Phil Coangelo, Pharm.D., Ph.D.
Doria (Woody) Dubois, Ph.D., CDRH/DCLD, Microbiology Branch Chief
Jeff Fritsch, CDER/HFD-590, Project Manager
Ravi Harapanhalli, Ph.D., CDER/HFD-160, Chemistry Reviewer
Eldon Leutzinger, Ph.D., CDER/HFD-160, Chemistry Team Leader
Joette Meyer, Pharm.D., CDER/HFD-590, Clinical Pharmacology and Biopharmaceutics Reviewer
Rigoberto Roca, M.D., CDER/HFD-590, Medical Team Leader

ORIDION MEDICAL LTD.
Sandy Brown, Manager, Regulatory Affairs
Edna Wellner, Ph.D., Director, Quality Assurance
Yacov Bubis, Vice President, Chief Operating Officer

[ ] Director, Regulatory Affairs, [ ]
[ ] Consultant (Affiliate), [ ]
[ ] . Consultant (Regulatory Affairs) [ ]

Presentation and Discussion

The following is a summary of the key issues discussed.

After introductions, Dr. Wellner began the meeting with a brief discussion of the contents of the Briefing Document and the questions Oridion would like the Agency's responses to.

Responses to Specific Questions Presented in the Briefing Document

Questions

a. Along with the manufacturing information for the drug product made at — there will be — months stability data in the original application. Will the Agency accept the NDA submission for filing with — as the drug product manufacturer?

Answer

Stability data on 2 additional batches will be required [ ] One of the 2 additional bathes can be smaller than pilot batches. These batches have to be manufactured using equipment similar to that used for the full size batches.

For NDA submission,— months real time and accelerated data on all — batches must be included.

Expiration date will be according to real time data available at the time of the NDA approval.

MINUTES OF AUGUST 17, 2000 MEETING (9:30 to 11:30 am)

ORIDION MEDICAL, LTD. WITH CDER DIVISION OF SPECIAL PATHOGENIC AND IMMUNOLOGIC DRUG PRODUCTS AND CDRH – DCLD – MICROBIOLOGY BRANCH

FDA will evaluate the totality of the data (including the — data) and may agree to a — months "temporary" expiry date. FDA will also consult with the stability committee.

b. The new — tablets will not be used in clinical studies. Information on dissolution profiles of the — tablets, and comparative dissolution testing with — tablets, will be provided in the NDA submission. Based on using the identical formulation, and the similarity of the manufacturing process, we expect rapid dissolution of the tablets. For this diagnostic agent, does the agency agree that tablets made at — and — can be considered equivalent and a bioequivalence study will not be required?

Answer

While FDA agrees with this proposal in theory, they require a review of the comparative dissolution profiles of [ ] tablets using the F2 statistic prior to committing to grant a waiver for bioeqivalence studies. The data may be submitted before the application.

FDA requested that dissolution be done in a media with a range of pH levels, including a citric acid buffer which has the same pH as the cirtica solution. The range of the pHs should encompass the pH of the citrica. Following this one time study the optimal pH level should be selected and then used in the manufacturing control test for the Finished Product. The use of media volume of 500 ml will require justification.

c. Does the agency agree that [

]

Answer

Oridion will try to obtain, from — the rationale for [

]

d. Does the agency agree that the stability data package ([ ] information) available at NDA submission is sufficient for filing the application, with the provision that Oridion will provide stability updates on the — tablets during the NDA review process?

Answer

The agency will accept the NDA with —months stability data on —batches produced at [ ] and will accept updates during the review time (also see answer to question a).

e. Does the agency agree that the [ ] information is adequate for filing the NDA?

Answer

The agency was concerned about [ ] Aspartame at [ ] FDA requires that the citrica will be put on stability at 30°C/60% RH. The NDA will include the data available at

The Agency requested that Oridion adds an identification test to the citrica. The Agency requires a stability indicating method or rationale for not using one.

f. Does the Agency agree that the stability information on the Citrica – of —months provided in the NDA and then followed by — month data provided during the approval process is adequate for filing the NDA?

Answer

The agency is willing to accept the stability information that will be present at submission and updates in the review process. See answer to question e.

Additional comments:

- Acceptance of 13C Urea at — is based on certificate of analysis and identity testing. The agency requires that released tests for the raw material for the first 3 production batches, will include determination of the isotopic ratio.
- [ ] test should be included as an In Process Control during manufacturing. [ ] should be included in the [ ] specifications including stability testing.
- All manufacturing sites must be ready for inspection at the time of submission.
- All processes and analytical methods have to be fully developed, established and validated according ICH and USP guidelines.
- A list of establishments, registration numbers and their readiness for inspection has to be included in the NDA.
- FDA requested that the labeling includes "manufactured by:...." And "manufactured for...." statements.
- FDA requires that we prove that the tablets used for the clinical trials are from batches identical to those that we have data on.
- Oridion is establishing an office in the US. This US office will act as the agent for the NDA. The holder of the NDA will be the Oridion office is Israel. [ ] is assisting Oridion with the NDA and is functioning as their liaison until the NDA is filed.

Please note that the overheads presented by Dr. Wellner during the meeting are attached to these meeting minutes.

12 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 08/15/01	**DUE DATE:** 10/15/01	**OPDRA CONSULT #:** 01-0185

TO: Mark Goldberger, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products
(HFD-590)

THROUGH: Yoon Kong
Project Manager
(HFD-590)

PRODUCT NAME:	**DISTRIBUTOR:**
IDkit-hp™ contains the following: 1 ^{13}C-Urea tablet, 75 mg 1 packet of Citrica, 4.5 g (citric acid) 1 IDcircuit™ cannula 1 drinking straw **NDA #: 21-314**	Oridion Medical 1987, Ltd.

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Special Pathogen and Immunologic Drug products, OPDRA conducted a review of the proposed proprietary name, IDkit-hp™.

OPDRA RECOMMENDATION: OPDRA has no objections to the use of the proprietary name, IDkit-hp™. See review for details.

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **October 5, 2001**

NDA NUMBER: **NDA 21-314**

NAME OF DRUG: **IDkit-hp™ contains the following:**

1 ^{13}C-Urea tablet, 75 mg
1 packet of Citrica, 4.5 g (citric acid)
1 IDcircuit™ cannula
1 drinking straw

NDA HOLDER: **Oridion Medical 1987 Ltd.**

I. INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug products (HFD-590), for assessment of the proprietary name of a diagnostic kit, "**IDkit-hp™**," regarding potential name confusion with other proprietary/generic drug names. In addition, the container label, carton and package insert labeling were also submitted for review of possible interventions in minimizing medication errors.

PRODUCT INFORMATION

IDkit-hp™ is a component of the BreathID™ system, which is a non-radioactive, in vivo, diagnostic test for the identification of patients with *Helicobacter pylori* infection. The BreathID™ system contains BreathID™ device, IDcheck™, and IDkit-hp™. The IDkit-hp™ breath test kit contains the following:

1 ^{13}C*Urea tablet, 75 mg
1 Citrica, 4.5 g (citric acid)
1 IDcircuit™ cannula
1 drinking straw

IDkit-hp™ is intended for use as an aid in the initial diagnosis and post-treatment monitoring of *Helicobacter pylori* infection in adult patients. The test may be used for monitoring treatment if used at least four weeks following completion of H. Pylori therapy. The packet of Citrica and a urea tablet must be reconstituted with 200 mL of tap water. The patient must drink this solution within two minutes of the test. The urease produced by H. pylori decomposes ^{13}C-Urea to $^{13}CO_2$ and NH_4^+ in the highly acidic environment of the stomach. This $^{13}CO_2$ is absorbed into the blood and then exhaled in the breath. This results in an increase in the ratio of $^{13}CO_2$ to $^{12}CO_2$ in a test breath sample compared to a baseline sample taken before the Urea/Citrica solution was

consumed. The BreathID™ device measures changes in the $^{13}CO_2$ to $^{12}CO_2$ ratio of exhaled breath. This device is for use by trained health care professionals.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound-alike or look-alike IDkit-hp™ to a degree where potential confusion between drug/device names could occur under the usual clinical practice settings. A search of the electronic online version of Thomson and Thomson and the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v,vi]. An expert panel discussion was conducted to review all findings from the searches. Because the proposed product, IDkit-hp, is a component of a drug/device system to be used only in the clinical settings, no prescription simulation studies were conducted.

A. EXPERT PANEL DISCUSSION

The Expert Panel discussion was conducted by OPDRA to gather professional opinions on the safety of the proprietary name, IDkit-hp™. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical, regulatory, and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. No product name was identified that was noted to have significant sound-alike or look-alike qualities relative to IDkit-hp™. The Expert Panel noted that "hp" is a common abbreviation for "H. Pylori" and "high potency." However, from a safety perspective, the panel did not object to the proposed name, IDkit-hp™, since it is a diagnostic kit to be used only in a clinical setting.

2. A representative from DDMAC did not have any concerns about the name with regard to promotional claims.

B. SAFETY EVALUATOR RISK ASSESSMENT

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[i] *MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300,* Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[ii] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iv] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[v] Data provided by Thomson and Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com.

[vi] WWW location http:// www.uspto.gov/tmdb/index.html.

In reviewing the proprietary name, IDkit-hp™, there were no drug product names identified by the Expert Panel that were thought to have significant sound-alike or look-alike qualities relative to the proposed name. The Expert Panel noted that "hp" is a common abbreviation for "H. Pylori" and "high potency." However, from a safety perspective, the panel did not object to the proposed name, IDkit-hp™, since it is a diagnostic kit to be used only in a clinical setting to measure *H. pylori.*

For these reasons, we do not object to the use of the proprietary name, "IDkit-hp™."

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container label, carton labeling, and the package insert of IDkit-hp™, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user errors.

A. CARTON AND CONTAINER (CITRICA)

The quantitative amount of Citrica is incorrect and should be revised to reflect 4.5 grams of Citrica, not 4.5 grains.

B. PACKAGE INSERT

No comments.

IV. RECOMMENDATIONS

1. OPDRA has no objection to the use of the proposed name, IDkit-hp™.
2. OPDRA recommends implementation of the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim, Pharm.D. at 301-827-0925.

/S/

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention

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/s/

Hye-Joo Kim
10/15/01 08:25:02 AM
PHARMACIST

Jerry Phillips
10/15/01 08:28:44 AM
DIRECTOR

Martin Himmel
10/15/01 10:54:05 AM
MEDICAL OFFICER

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

REQUEST FOR CONSULTATION

Division/Office): OPDRA, HFD-400

FROM: Mark Goldberger, M.D. , Division Director of Special Pathogen and Immunologic Drug Products, HFD-590

THROUGH: Yoon Kong, Pharm.D., Regulatory Project Manager, HFD-590

DATE: August 15, 2001	IND NO.	NDA NO. 21-314	TYPE OF DOCUMENT: original NDA submission (N 000)	DATE OF DOCUMENT: February 2, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
[ ]	Standard	Drug-Device for *H. pylori*	October 15, 2001

NAME OF FIRM: OridionMedical 1987 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:

The sponsor is asking for the tradename of their drug-device product to be [ ] The device part of this application (510K application) has been reviewed and approved on July 9, 2001. Because this application calls for a joint review between CDER and CDRH, please just focus on the drug aspect of this product. Once an OPDRA reviewer has been assigned to this application, we will contact the sponsor and have them send the necessary materials to the assigned *OPDRA reviewer. The 10-month PDUFA date on this* application is December 2, 2001. If you have any questions or need more information, please contact Yoon Kong @7-2127.

SIGNATURE OF REQUESTER Yoon Kong	METHOD OF DELIVERY (Check one) ■ E-MAIL (DFS) ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Yoon Kong
8/15/01 02:22:48 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

M1

JUL - 9 2001

Mr. Sandy Brown
Regulatory Affairs Manager
Oridion Medical 1987 Ltd.
7 HaMarpe Street
Har Hotzvim Industrial Park
P.O. Box 45025
Jerusalem, Israel

Re: K011668
Trade Name: Oridion BreathID™ System for *Helicobacter pylori*
Regulation Number: 866.3110
Regulatory Class: I
Product Code: MSQ
Dated: May 14, 2001
Received: May 17, 2001

Dear Mr. Brown:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments. You may, therefore, market the device, subject to the general controls provisions of the Federal Food, Drug, and Cosmetic Act (Act). The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, and labeling, and prohibitions against misbranding and adulteration.

In addition, we have determined that your product contains the following component subject to regulation as drugs: ^{13}C-enriched urea tablet-75mg.

Our substantially equivalent determination does not apply to the drug component (NDA 21-314) of your product. For information on applicable Agency requirements for marketing this product, we suggest you contact:

Mark Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval) it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, FDA will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, the Food and Drug Administration (FDA) may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under section 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification although we recommend that you first contact the Center for Drug Evaluation and Research before marketing your drug component[s]. An FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and permits your device to proceed to the market, but it does not mean that FDA approves your device. Therefore, you may not promote or in any way represent your device or its labeling as being approved by FDA. If you desire specific advice for your device on the labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), promotion, or advertising, please contact the Office of Compliance, Promotion and Advertising Policy Staff (HFZ-302) at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or (301) 443-6597, or at its internet address "http://www.fda.gov/cdrh/dsmamain.html".

Sincerely yours,

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Oridion

June 10, 2001

Indications For Use

510(k) Number (if known): K011668

Device Name: BreathID™ System

Indications For Use:

The BreathID™ System is used to diagnose and monitor *Helicobacter pylori* infection by measuring changes in the $^{13}CO_2/^{12}CO_2$ ratio in a patient's breath following the ingestion of ^{13}C urea.

The Oridion BreathID™ system continually and non-invasively measures changes in the $^{13}CO_2/^{12}CO_2$ exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori* infection in the stomach. The Oridion BreathID™ System is to be used as an aid for initial diagnosis and post treatment monitoring of *Helicobacter pylori* infection.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use X OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)

Woody Dubois
(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K011668

Oridion Medical 1987 Ltd. • POB 45025 • Jerusalem 91450 Israel • Voice:+972 2 589-9115 • Fax:+972 2 582-8873

Telephone Memorandum

To: File, K011668

From: Review Scientist, Bacteriology Devices Branch, Division of Clinical Laboratory Devices.
HFZ-440

Date: March 8, 2001

Re: Oridion Medical BrathID™Test Systems

Conversation With:

Oridian Diagnostics: Sandy Brown, Terry Brady, Yacov Bubis, Ilan Ben-Oren, Edna Wells, Antonis Koutsoukos, [ ]

FDA Participants: Woody Dubois, Freddie Poole

FDA provided guidance to Oridion on the type of information needed to support the safety and effectiveness of the Oridion BreathID™ Test System. The issues in the K9 letter issued on February 14th were discussed.

Reproducibility data: The study submitted by the firm appeared to be adequate for doing instrument reproducibility, but would not demonstrate the reproducibility of the breath sample because artificial standard gases would be used. We recommended that they consider using a minimum of three patients sent to three different sites. Oridion agreed that it could be done. They would outline a study and submit for FDA's comments.

The **Interference Study** proposed was Ok.

Cut-off Study: We agreed to accept the data from the Hadassah study that was used to determine the initial cut-off value.

Sensitivity and Specificity Study: Oridion agreed to review the recommendations of the FDA statistician on the presentation of sensitivity and specificity, the non-evaluable data, and the calculation of data using the one-sided analysis.

The firm informed us that they had conducted pre-clinical studies in Hadassah and at the Wolfson Clinic in Jerusalem. Because the Meretek UBT test was not read using the Gas Mass Spectrophotometer as recommended by Meretek, they were not submitted. We informed them that they could be submitted as supplemental studies.

Oridion agreed to submit a copy of revised protocols and data. We agreed to review and comment. The Oridion statistician agreed to consult with the FDA statistician.

CDER also provided comments for the Post-Therapy Treatment studies.

Freddie M. Poole

From Sponsor

MINUTES

MEETING OF ORIDION MEDICAL, LTD. WITH DCLD-MICROBIOLOGY BRANCH, CDRH AND CDER

MARCH 16, 2000 (1:30 to 3:15 pm)

LIST OF ATTENDEES

FDA

Doria (Woody) Dubois, Ph.D., CDRH/DCLD/Microbiology, Branch Chief
Robert Hopkins, M.D., CDER, Medical Officer
Karen Higgins, DSPIDP/OB/DBIII
Joette Meyer, M.D., CDRH/ODEIV/DSPIDP
Emil Wang, CDRH/DCRD/Anesthesiology/Defilrillator Devices, Scientific Reviewer
Harry Bushar, CDRH/OSB/DBS
Freddie Poole, CDRH/CDLD/Microbiology, Scientific Reviewer
Jeff Fritsch, CDER/HFD-590/Project Manager
Brian Harvey, CDRH/ODE/DCLD
Rari Harapanhalli, Ph.D., CDER, Chemistry Reviewer

ORIDION MEDICAL LTD.

Sandy Brown, Manager, Regulatory Affairs
Daniel Katzman, Manager, Business Development, Breath Test Business Unit
Edna Wellner, Ph.D., Director, Quality Assurance
Yacov Bubis, Vice President, Chief Operating Officer
[ ] Consulting
Donna L. Ward, M.B.A., M. S., Associate Director, Regulatory Affairs
Suzanne Pohlmann, M.S., Regulatory Specialist, Regulatory Affairs

Presentation and Discussion

The following is a summary of the key issues discussed.

After introductions, Dr. [ ] began the meeting with a brief overview of Oridion. Dr. Dubois forewarned Oridion that all questions might not be answered today due to the limited amount of the time the Agency had to review the briefing document. However, he did indicate that the Agency would provide Oridion with responses to all questions.

Mr. Brown provided a brief introduction of the BreathID System. He indicated that the technology created by Oridion Systems had been adapted to measure C_{12}/C_{13} ratio for the BreathID System. Mr. Brown clarified that although the device does not normally require calibration it is equipped with a System Check which serves as a control feature. In addition, Mr. Brown presented the protocol and its amendment that allowed patients previously excluded from the study due to the administration of PPI blockers to participate in the study.

A number of issues were raised during Mr. Brown's presentation and discussed, as noted below:

Dr. Harvey indicated that he was concerned that patients taking PPI blockers were allowed to participate in the study. He felt that this may result in a higher number of false negatives because PPI blockers have been reported in the medical literature as having the ability to stun H. pylori by temporarily halting the production of urease. Mr. Katzman indicated that the histology results obtained from patients have agreed with urea breath test (UBT) results. That is, false negative results, due to PPI usage, have not been reported. Mr. Katzman also stated that an interim analysis of the study has shown that of the 22 patients testing positive, there was 100% agreement with all tests done on pre and post-therapy patients. Dr. Harvey asked how long after treatment post-therapy tests were performed and Mr. Katzman indicated 4 to 6 weeks later. Mr. Katzman further clarified that although results may be obtained 6 minutes after using the BreathID, during the clinical study measurements continued for a total of 20 minutes. If results obtained after 20 minutes are close to the threshold values, then measurements continue for an additional 10 minutes.

Dr. Dubois emphasized that Oridion should not rely on histology results alone. He stressed the need for the results from histology, as well as the other tests to be in agreement. He indicated that if the results were not in agreement, then the patient should not be enrolled.

Dr. Dubois asked whether there were different cut off values for the determination of a positive or negative result. Mr. Katzman explained that the cut off value is always the same; a result of 5 at 20 minutes and if the result is between 4-6, then the device would continue to monitor the patient for another 10 minutes. At the 30-minute timepoint, the threshold is 5.

Dr. Hopkins asked Oridion about the absence of a pediatric trial. He referred Oridion to CFR 314.55 (outlines the requirement for pediatric data). He stated that since the BreathID System does not involve a new molecular entity, it would be possible for Oridion to request a waiver or deferral for a pediatric study when the NDA is submitted. He also stated that if Oridion did not intend to submit pediatric data, then Oridion should try to submit the application before Dec 2, 2000. Dr. Hopkins warned that the FDA may refuse to file an application that does not contain pediatric safety data if it is submitted after Dec 2, 2000.

Next, Dr. Wellner presented information regarding the Chemistry and Manufacturing Control section of the application. Dr. Wellner indicated that the stability study for urea tablet would be completed in June 2000 and the data would support [ ] shelf-life. Dr. Wellner indicated that study results demonstrated that C13-urea was stable for a minimum of 2 hours when prepared in a 200 ml Citrica solution. She further indicated that due to the nature of the substrate in the solution, a standard HPLC [ ] method was used for the this stability study and that Oridion, due to the limited application of these data, planned to conduct a partial validation of this method for the NDA (precision and linearity). Dr. Wellner then asked if the Agency agreed with this approach. Dr. Harapanhalli asked what Dr. Wellner meant by "limited validation" of urea stability. Dr. Wellner indicated that the current validated method for the assay of Urea is [ ] HPLC method, which could not be used due to [ ] the solution (urea tablet and Citrica). Therefore, Oridion used an alternative method to measure stability, [ ] method. Dr. Harapanhalli asked if this method could measure any degradation products of urea and Dr. Wellner indicated that with this method, urea has been shown to be stable for up to two hours by showing no decrease in the Urea concentration in the solution . Dr. Harapanhalli asked if Oridion had tried [ ] and Dr. Wellner indicated that this had not been tried. Dr. Harapanhalli indicated that he would need to review the data before determining whether this method was acceptable for assessing the stability of urea.

Dr. Harapanhalli indicated that the inspection of the manufacturing facility typically slows the NDA review process. However, it would help if Oridion provided him with the names and addresses of the facilities where the drug(s) are manufactured, case file numbers, and drug registration numbers, as well as the dates they were last inspected.

In regards to the 510K application, Mr. Wang requested that Oridion include descriptions of all modifications to approved technology, as well as descriptions of all hardware and software modifications made to accommodate the device technology. In addition, the application should include information about the electromagnetic compatibility and electronic safety, as well as information about the device's intended environment.

Mr. Wang also asked how the modified product relates to the current capnograph technology. Mr. Brown indicated that [ ] safety testing had been done and that the device would not be placed in a clinical environment during the clinical study unless it met these standards. Mr. Wang suggested that Oridion see the Reviewer Guidance for Premarket Notification Submissions (Nov, 1993) written by the Anesthesiology and Respiratory Devices Branch for further guidance. He further suggested that integration testing be performed and stated that the device should be tested under maximum — conditions. Lastly, Mr. Wang commented that the BreathID system will take on a Class II designation.

Discussions Regarding Specific Questions Presented in the Briefing Document

510(k) Questions

a. Does the Division agree that the Table of Contents for the 510(k), as outlined in this Briefing document, is acceptable?

   Dr. Dubois indicated that Oridion needs to provide the clinical data in both the NDA and 510(k) applications. Mr. Brown indicated that the protocol and all data would be in both applications. Dr. Dubois also indicated that the non-clinical studies, including the cut-off studies and reproducibility studies would need to be in the 510(k). Dr. Dubois suggested that Oridion use the Meretek package information as an example of what the FDA would expect to see. Mrs. Poole indicated that a 510(k) statement, as well as a statement regarding the intended use of the device needed to be in the 510(k) application.

   Dr. Hopkins reiterated the need for Oridion to address the Pediatric Final Rule and financial disclosure in both the 510(k) and the NDA applications.

b. Based on current enrollment (as of Mar 3, 2000, 40 positives out of 258 patients enrolled) in the pivotal clinical trial being conducted in the US, Oridion anticipates only about 50 patients testing positive for *H. pylori* will be enrolled in the trial. Does the Division believe that this will be an adequate sample size for positive patients?

   Dr. Meyer indicated that the BreathID test should demonstrate pre-therapy confidence intervals that were the same or better than the — test which is based on the same principle. This means that the BreathID will have to have a lower limit of — and a specificity of — for 95% confidence. Dr. Meyer indicated that this translates into the results for the BreathID test for 48 out of 50 patients being in agreement with the results from the other testing methods. We also discussed the fact that the post eradication claim is essential for Oridion. Oridion will apply the same analytical principle to the post eradication data defined in the clinical protocol.

c. Although the BreathID™ System will be used to measure and compute the $^{13}CO_2$ to $^{12}CO_2$ ratio, the technology used in this device is identical to Oridion's capnographs already approved to continuously and non-invasively measure and monitor the concentration of CO_2 in the expired and inspired breath of patients. To date, all of Oridion's CO_2 breath measurement devices [device classification name = analyzer, gas, carbon-dioxide, gaseous-phase: Microcap (K981114), Microcap/NPB-75, combined Capnograph/Pulse Oximeter monitor (K964239), Gemini (K950387) and Polaris (K950388) have been classified as Class II Devices under 21CFR868.1400. Based on the classification of other *Helicobacter pylori* breath tests [Meretek's Breath Test for *H. pylori* Collection Kit (K95220) and Alimenterics Lara ™ Breath Test System (K973000)], Oridion believes that their BreathID™ Test System, which uses Oridion's Microstream Nasal Cannula Filterline (K980325), should be classified as a Class I Device under 21CFR866.3110 (product code LYR = Campylobacter pylori). Does the FDA agree with this?

Mr. Wang indicated that the BreathID System will be classified as a Class II Device.

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Questions

Urea & Citrica

Product

NDA Questions

a. Does the Division agree that the Table of Contents for the NDA, as outlined in this Briefing Document, is acceptable?

The Agency indicated that based on a quick review it appeared to be acceptable.

b. It is the intention of Oridion to provide each Division with the following information electronically:
   - SAS data sets for the pivotal clinical study conducted in the United States.
   - Proposed labeling in WORD (version 7.0).

The Agency also requested that the clinical study reports and CMC information be provided in WORD. With regards to the full study reports, Ms. Ward indicated that the text of the front end of the reports would be provided in WORD, but that all appendices might not be available in WORD, however those available would be provided.

c. As the number of deaths and dropouts due to serious adverse events is expected to be very small, and these will be discussed in the NDA, Oridion would like to not include Case Report Forms (CRFs) in Section 13 of the NDA, but rather provide them upon the Agency's request. Does FDA agree with this approach?

The Agency agreed that CRFs do not have to be submitted. However, Dr. Meyer emphasized that Oridion would need to provide CRFs for deaths and drop-outs in the NDA.

d. Where and when would CDER like the CMC/Method Validation information provided to the field office?

When the Agency has completed its review, it will inform Oridion where to submit the field office copy.

e. Does the Agency agree with the approach taken with regards to the CMC aspects of this product, as described in this Briefing Document?

The Agency, as noted, would like additional time to review the information provided and is willing to discuss the CMC aspects of this application.

NDA Exclusion Requests

a. Pediatric studies.
No pediatric subjects have been included in this study.

As noted, Oridion needs to address the information needed as per the Pediatric Final Rule.

b. Integrated Summary of Safety (ISS)
Oridion would like to request that the inclusion of an ISS in the NDA be waived. They believe that based on:
   (1) the data presented in this Briefing Document,
   (2) the fact that there have been very few, if any, safety issues reported in association with the use of ^{13}C-urea in UBTs, and

(3) there is only one pivotal and four supporting clinical studies to be presented in the NDA and 510(k) applications,

an integration of the safety databases is not necessary. Oridion will discuss and compare all available safety data in each study report and in the text of the application.

The Agency agreed.

c. Integrated Summary of Efficacy (ISE)*

Oridion would like to request that the inclusion of an ISE in the NDA be waived. They believe that based on:

(1) the data presented in this Briefing Document,
(2) there is only one pivotal clinical study being presented in the NDA and 510(k) applications, and
(3) approval for the use of this product will be based on a 510(k) submission.

an integration of the efficacy databases is not necessary. Please note that Oridion will still discuss and compare all available efficacy data in the text of the application(s).

The Agency agreed.

d. 120–Day Safety Update

As only one pivotal trial will provide the data to support the safety and "effectiveness" of this product, Oridion would like to request that the requirement for the 120-Day Safety Update be waived. However, Oridion will submit final study reports to the NDA for all trials noted to be ongoing in the marketing applications.

The Agency agreed.

e. Microbiology Section

As Oridion believes this device/drug product combination is a diagnostic product, Oridion would like to request that the requirement for a Microbiology Section in the NDA be waived.

The Agency agreed.

Additional Discussions

Mr. Bubis asked if the Agency could estimate the review time for an application such what Oridion plans to submit. Dr. Dubois indicated that, based on past history the average review time for a 510(k) is 70 days, provided all information is appropriately submitted. However, the release of the substantially equivalent letter would depend on the NDA. Dr. Dubois indicated that a GMP inspection can typically delay a NDA review/approval. Mr. Brown indicated that he believed the FDA had already inspected the manufacturing facility. The Agency pointed out that they typically request an inspection of the manufacturing facility when the NDA is filed and if there are no problems, (i.e. all information had been submitted in the correct format), then it might be possible that the NDA could be reviewed within 2 to 3 months and that the inspection might be scheduled 3-4 months after NDA submission..

* Efficacy = effectiveness in diagnosis.

Dr. Meyer provided Oridion with copies of tables to complete regarding the number of pre-treatment patients receiving the CLO test, histology and BreathID test. Dr. Meyer also stated that the tables should include both evaluable and non-evaluable patients. Lastly, Dr. Meyer suggested that Oridion look at the Meretek label for post-therapy treatment.

Dr. Hopkins stated that before the NDA, Oridion should propose a statistical plan for post-therapy patients. The plan should include approximately 70 patients tested using BreathID; half of these results should be compared to the Meretek test results and the second half should be compared to histology and CLO test results. Dr. Meyer stated that they would not expect Oridion to have the same number of patients as Meretek due to the fact that the purpose of the study was to test the efficacy of the drug as a treatment. Furthermore, the drug in the Meretek study did not work well and therefore produced an unusually high number of positive patients following treatment.

The FDA would accept either the endoscopy or Meretek test as the gold standard. Therefore, they should combine the Meretek and endoscopy results into a single database.

Note: there was a post-meeting request to provide the Agency with the analysis plan for the post-treatment phase of the study.

Regarding the CMC section, Dr. Wellner indicated that based on her conversation with Dr. Harapanhalli, the FDA wants Oridion to establish a [redacted] testing procedure for the Urea tablets, and that this should be included in the NDA.). Dr. Wellner indicated that although testing should include at least the three first batches accepted by Oridion , the Agency will accept that only one batch will be included in the NDA because Oridion only has usedone batch for the clinical study.. In addition, Dr. Wellner indicated that Dr. Harapanhalli wants more information on the Citrica (what was presented in the Briefing Document is not enough).

Note: A copy of the overheads presented are attached to the minutes, as is the clarified page of the briefing document left with Mrs. Poole.

Reviewed and approved by Oridion 25-5-00

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MINUTES

MEETING OF ORIDION MEDICAL LTD. WITH DCLD – MICROBIOLOGY BRANCH

March 11, 1999

ATTENDEES

FDA

Doria (Woody) Dubois, Ph.D., CDRH/DCLD/Microbiology, Branch Chief
Joseph Hackett, Ph.D., CDRH/DCLD, Associate Director
Freddie Poole, CDRH/DCLD/Microbiology, Scientific Reviewer
Marion Heylinger, CDRH/DCLD/Microbiology, Scientific Reviewer
Emil Wang, CDRH/DCRND/Anesthesiology/Defibrillator Devices, Scientific Reviewer
Robert Hopkins, M.D., CDER, Medical Officer
Robin Anderson, CDER, Chemistry Reviewer
Ravi Harapanhalli, Ph.D., CDER, Chemistry Reviewer

ORIDION MEDICAL LTD.

Sandy Brown, Manager, Regulatory Affairs
Daniel Katzman, Manager, Business Development, Breath Test Business Unit
Gustavo Auerbach, Manager, Clinical Trials Project
[ ] : Consulting

The meeting began at 9:30 AM with self-introduction of all attendees. The following is a summary of the important points raised and addressed at the meeting.

- Dr. Dubois initiated the meeting with a brief summary that as a combination product, the BreathID System device would be reviewed in CDRH/DCLD/Microbiology, while the urea drug portion of the system would be reviewed in CDER. The CDER review would be subject to payment of a user fee. However, CDRH/DCLD would be the Lead Review Center.
- Sandy Brown (SB) presented a brief overview of Oridion, including the fact that the company, under the name Spegas, has FDA clearances for several capnography devices.
- Daniel Katzman (DK) presented an overview of the BreathID System, with a discussion of the technology involved. Questions were asked regarding the capability of the device to discriminate between ^{13}C and ^{12}C in breath CO_2. DK and SB explained how this was accomplished. DK also summarized the information concerning the urea drug included in the system, its raw material supplier and manufacturer. No untoward questions were raised, and the CDER representatives

were comfortable with the raw material supplier being the same as for the legally marketed Meretek *H. pylori* assay system.

- Gustavo Auerbach (GA) presented slides which summarized the Clinical Trial Protocol.

General discussion followed the Oridion presentation which centered on the BreathID device, the clinical protocol, and the urea drug. These questions and responses are summarized below:

BreathID Device

- Dr. Dubois asked how the device is calibrated. DK explained [ ]

  which are involved in the calibration of the device on a routine basis.
- Dr. Dubois asked whether or not the device has been exposed to smokers and other patient types who produce breath containing materials which may interfere with the system. SB and DK emphasized the detector device is set to only detect ^{13}C and ^{12}C, and will not recognize or detect any other material in the breath.
- Dr. Dubois asked if there is an established cut-off point for positive, negative or equivocal samples? DK indicated that of the 189 patients in the Feasibility Study conducted in Israel in mid-1998, none were found to be equivocal, but rather all were negative or positive, and all results showed 100% agreement with Mass Spectrometry. In the clinical trial, however, the data obtained will be used for establishing cut-off criteria.
- Ms. Poole and Dr. Dubois asked about the [ ] statement made in the Oridion presentation. [ ] explained that in FDA terms, [ ] typically implies that the system can and will be used in many settings in a hospital, medical clinic, etc. However, Oridion's meaning of [ ]' is that a sample is collected and analyzed immediately while the patient is still sitting next to the system. This is opposed to previously cleared urea breath test devices where a breath sample is collected in a collection device, and then shipped to a location at which an analysis device will analyze the breath sample. — suggested Oridion might want to replace the phrase [ ]' with other words indicating the result is obtained immediately. Also, with [ ] claim, FDA would expect that in the clinical trial, data will be collected from all sites (e.g., emergency room, patient bed side, intensive care unit, etc.) where the system might be utilized, and the data will be collected by the typical personnel who work at each [ ] site.
- Dr. Hopkins asked if training would be provided to operators before their use of the system. DK indicated a one-day training session would be included with the sale of each device.
- Dr. Dubois asked if the software in the system would be properly validated. SB indicated the software would be validated and verified as per the most recent draft FDA Reviewer Guidance Document for Software in Medical Devices.
- Mr. Wang indicated Oridion needs to ensure the system is tested according to various electrical and safety standards accepted in the U.S. and abroad. He cited the standard

number for those performance standards of particular interest. — will email Mr. Wang in order to request a list of the standards he had specifically mentioned the system should be tested to.

Clinical Protocol

- [

]

- Ms. Poole and Dr. Dubois asked about the 100 patients who would be entered into the post-therapeutic follow up portion of the trial. If there is eradication of the *H. pylori* after treatment of these 100 patients, one would not expect to find many positive samples in this group. Would that be a problem? Dr. Hopkins stated that with the experience he and CDER have developed with breath urea devices, he did not see this as a problem since there are few eradication failures, but that the large number of positive samples from the pre-therapeutic portion of the trial (approximately 50% of the 250 patients entered into the study at 2 sites – 1 in the U.S. and 1 in Israel) would validate the capability of the system to detect positive samples. — added that from the device point of view, it only indicates a positive or negative result, regardless of whether it is a pre- or post-therapeutic specimen. For the post-therapeutic portion of the clinical study, Oridion intends to supplement, if necessary, additional post-therapeutic specimens to reach 100 specimens total. The additional specimens would come from other *H. pylori* positive patients who have recently completed post-therapeutic treatment.
- Dr. Dubois asked about the total time for the test. GA and DK explained that a definitive result may be obtained in 6 minutes. In fact, the Feasibility Study showed 2/3 of the patients already have definitive results (either positive or negative) in 6 minutes and 90% in 10 minutes. The default test time is 20 minutes, but the test can be stopped by the operator when a definitive result is achieved. Results from the clinical trial will be reviewed to determine if an algorithm for a shorter test time can be established and implemented. On the other hand, if at the end of 20 minutes the result is close to the threshold, the test can be continued until a definitive result is achieved.
- The clinical trial protocol was felt to be satisfactory as presented, with inclusions of the notations and ideas presented above.

Urea Drug

- Dr. Harapanhalli presented Oridion with a 2-page summary of the various regulatory criteria the NDA (New Drug Application) will be measured against, and Ms. Anderson further indicated Oridion is responsible for ensuring all other aspects of an

NDA not covered in the Dr. Harapanhalli's paper are addressed in the NDA. DK indicated the [ ] manufacturer has already prepared much of the materials presented in their dossier of the product for Europe. However, Oridion will ensure all required materials will be present in the NDA.

- Dr. Harapanhalli indicated information must also be provided for the citric acid, colorants, or any other materials which are part of the urea tablet. He was not certain how citric acid is regulated. — will provide this information to Oridion.
- It is expected the NDA may be the time-limiting portion of the system approval and clearance. — asked what the typical review times are currently for a well-prepared NDA, for a fairly well characterized product such as urea, which the agency is quite familiar with. Ms. Anderson indicated CDER is required to provide a decision to the sponsor within 9 – 10 months, which could be a significantly shorter time period for a well-prepared NDA. DK asked if Oridion can expect to obtain clearance for the device and approval for the drug at the same time. Ms. Anderson responded that while CDER is quite familiar with urea, the factors that generally result in an extended review are due to GMP deficiencies detected at the manufacturing site during the pre-approval inspection.

The meeting ended at 11:30 AM. Dr. Dubois and the CDER representatives indicated their continued willingness to assist Oridion, as needed, as the company continues to work toward approval/clearance of the BreathID System. Oridion is appreciative and grateful to CDRH and CDER for their assistance to date, and for setting time aside for this meeting.

Respectfully submitted,

[ ]

[ ]

Technical Adviser

[ ] Consulting

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Chief Mediator and Ombudsman
5600 Fishers Lane, (HF-7)
Rockville, MD 20857

Food and Drug Administration
Rockville MD 20857

April 6, 1998

Sanford Brown
Regulatory Affairs Manager
Oridion Medical Ltd.
Har Hotzvim Science Based Industrial Park
POB 45025
91450 Jerusalem, Israel

RE: Request for Designation
Oridion Breath ID Test Kit
Our File: RFD 98-03

Dear Mr. Brown:

We have completed our review of the above-referenced request for a product jurisdiction determination, accepted for filing on February 4, 1998.

The Oridion Breath ID Test Kit is a breath test system that consists of (1) a medical device for measuring and computing the ratio of $^{12}CO_2$ and $^{13}CO_2$ in a patient's exhaled breath and (2) a test kit that contains ^{13}C urea and a nasal cannula that is connected to the Breath ID device during the breath test. The breath test system is an in vivo diagnostic test for the identification of patients with Helicobacter pylori (H. pylori) infection.

Oridion stated that the information in the request for designation "shows CDRH should be the lead center" for review of the marketing application(s) for the test system.

After considering the information in the above-referenced request, and consulting with the appropriate officials in CDRH and the Center for Drug Evaluation and Research, we conclude that the Oridion Breath ID measuring device and the test kit together constitute a combination product whose primary mode of action is that of a device. As the primary mode of action of the combination product is that of a device, premarket review and regulation responsibility for the product is assigned to CDRH. The breath test system will be regulated by CDRH using both medical device and new drug review legal authority, as follows: (1) the test kit, including the ^{13}C urea drug component, will be reviewed and regulated under the new drug provisions of the Federal Food, Drug, and

Cosmetic Act (21 U.S.C. 355)[1]; and (2) the combination of the test kit and measuring device will be regulated and subject to review under the 510(k) premarket notification provisions of the medical device section of the Act.

Any clinical investigations of the system should be conducted under the investigational device provisions of the law (21 CFR Part 812); a separate investigational new drug application (IND) is not required.

Submissions for the system should be made to CDRH. The Division of Clinical Laboratory Devices (DCLD), Office of Device Evaluation, CDRH will be the primary review group. DCLD will conduct its review in consultation with review staff in CDER, as appropriate. DCLD will provide guidance on the format and content of all required investigational and marketing submissions. For further information, contact Kaiser Aziz, Associate Director, DCLD, CDRH, 2098 Gaither Road, HFZ-440, Rockville, MD 20850, or by telephone at 301-594-3084.

Please include a copy of this letter in future submissions to CDRH.

Finally, you should be aware that a new drug application for the test kit may be subject to user fees, in accordance with the requirements of the Prescription Drug User Fee Act of 1992. For questions about user fees, contact Mike Jones, Consumer Safety Officer, CDER, 1451 Rockville Pike, HFD-005, Rockville, MD 20852, or by telephone at 301-594-2041.

If you have any questions about this letter, please telephone me at 301-827-3390.

Sincerely yours,

Steven H. Unger
Deputy, Office of the Chief Mediator
and Ombudsman

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[1] Please note that ^{13}C Urea is covered by an approved new drug application. The new drug application for the drug product is covered by marketing exclusivity that expires September 17, 2001. FDA may not be able to accept an abbreviated application (ANDA) for the ^{13}C Urea drug product until expiration of the market exclusivity period. Eligibility of the product for ANDA review should be discussed with Gordon Johnston, Deputy, Office of Generic Drugs, CDER, 7500 Standish Place, HFD-601, Rockville, MD 20855, or by telephone at 301-594-0183.