# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER

# NDA 21-314

# Chemistry Review(s)

# NDA 21-314

## IDkit:Hp™
## (containing $^{13}$C-urea tablet for oral solution and citric acid powder for oral solution)

**Oridion Medical 1987 Ltd.**

**Mark R. Seggel**
**Division of Special Pathogen and Immunologic Drug Products**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-314

2. REVIEW #: 2

3. REVIEW DATE: 17-DEC-2002

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | February 2, 2001 |
| BL | July 8, 2001 |
| BL | October 10, 2001 |
| BC | October 24, 2001 |
| BC | November 6, 2001 |
| BL | November 12, 2001 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| AZ | June 26, 2002 |
| BZ | September 3, 2002 |
| BC | September 18, 2002 |
| BC | October 1, 2002 |
| BZ | October 1, 2002 |
| BC | November 3, 2002 |
| BC | November 17, 2002 |
| BL | November 21, 2002 |
| BL | November 27, 2002 |
| BL | December 4, 2002 |
| BL | December 16, 2002 |
| BL | December 17, 2002 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Oridion Medical 1987 Ltd. |
| Address: | 7 Ha Marpe<br>POB 45025<br>Jerusalem 91450 Israel |
| Representative: | Oridion Medical Inc.<br>77 Franklin St.<br>Boston, MA 02110 |
| Telephone: | 617-482-0818 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: IDkit:Hp™ (a component of the BreathID™ System)
b) Non-Proprietary Name: $^{13}$C-urea tablet for oral solution
citric acid powder for oral solution
c) Code Name/# (ONDC only): n/a
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50

10. PHARMACOL. CATEGORY: Diagnostic for *H. pylori* infection

11. DOSAGE FORM(S): $^{13}$C-Urea: tablet for oral solution
Citric Acid: powder for oral solution

12. STRENGTH/POTENCY: $^{13}$C-urea: 75 mg
citric acid: 4.0 g

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OTC

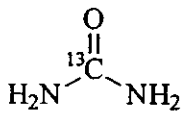
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$^{13}$C-Urea (99% enriched)
CAS Registry: 58069-82-2
Molecular Formula: $^{13}CH_4N_2O$
Formula Weight: 61.06



17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF# | Type | Holder | Item Referenced | Code | Status | Date Review Completed | Comments |
|---|---|---|---|---|---|---|---|
| [ | II | [ | [ $^{13}$C-Urea | 3 | Adequate[a] | 3/3/01 | LoA 8/10/00 |
| ] | III | ] | ] | 4 | N/A | last reviewed 2/16/01 | Contract<br>LoA 12/13/00 |

[a]Last reviewed March 3, 2001; some deficiencies related to method validation were noted, but the DMF was found adequate to support the manufacture of $^{13}$C-urea (see Chemistry Review of N20-586/SE2-004).

[b]Type I DMF resubmitted as Type III but does not contain specific CMC information. [ ] performs contract [ ] for a very large number of pharmaceutical companies. [ ] has acceptable cGMP status.

**B. Other Documents:** Not Applicable

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | - | | |
| EES | acceptable | July 9, 2001 | J. D'Ambrogio, HFD-324 |

Chemistry Review Data Sheet

| | | | |
|---|---|---|---|
| | acceptable | October 7, 2002 | S. Adams, HFD-324 |
| Pharm/Tox | - | | |
| Biopharm | revised dissolution acceptance criteria acceptable | October 15, 2002 | S. Jang, OCPB |
| LNC | - | | |
| Methods Validation | dissolution test acceptable unable to evaluate | December 14, 2001 | W. Charles Becoat |
| OPDRA | comments provided | October 5, 2001 | H.-J. Kim, Pharm.D. |
| EA | n/a | | |
| Microbiology | - | | |

# The Chemistry Review for NDA 21-314

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The deficiencies noted in the November 30, 2001 approvable letter with respect to the chemistry, manufacturing and controls for "Citrica," the citric acid-containing component of the IDkit-Hp™ have been adequately addressed. From the chemistry perspective it is, therefore, recommended that this New Drug Application, as revised, be approved.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is $^{13}$C-labeled urea, 99%-enriched. The chemistry, manufacturing and controls (CMC) of the drug substance were reviewed in Chemistry Review #1 of this NDA.

The drug product consists of a tablet containing 75 mg $^{13}$C-enriched urea and a packet of flavored citric acid powder (Citrica). The $^{13}$C-urea tablet CMC was reviewed in Chemistry Review #1 of this NDA. Additional stability data and dissolution data were provided in the resubmission. The dissolution test acceptance criteria has been revised. An expiration dating period of 30 months has been established for product stored at 25°C (USP Controlled Room Temperature).

Because of the numerous problems associated with the original formulation of Citrica (see November 30, 2001 AE letter), the citric acid containing component of the product has been reformulated. Ingredients include citric acid (4.0 g), aspartame and tutti frutti flavoring. Adequate documentation supporting the use of all the ingredients are provided in the resubmission. A new contract manufacturer [ ] has been hired. Validation batches have been manufactured and placed on stability. The manufacturing process is straightforward and appears to adequately controlled. The acceptance criteria have been revised as requested. Initial stability data are acceptable, but the shelf life remains limited by degradation of aspartame.

An expiration dating period of 12 months for product stored at 25°C (USP Controlled Room Temperature) has been established.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is used in combination with Oridion's BreathID™ System, a $^{13}C$-urea breath test. This system is primarily a diagnostic device for the detection of gastroduodenal *Helicobater pylori* infection. This device measures the ratio of $^{13}C$-carbon dioxide and $^{12}C$-carbon dioxide exhaled by the patient subsequent to administration of $^{13}C$-urea. Elevated levels of $^{13}CO_2$ are indicative of *H. pylori* urease enzyme activity. The test is performed entirely in a doctor's office or clinic. The device is based on isotope-specific infrared spectrometry and what is referred to as "molecular correlation spectrometry." A 510k for the device was recently approved by CDRH. The $^{13}C$-urea tablet and the flavored citric acid powder are dissolved in a glass of water (200 mL) for oral administration at the beginning of the test. The citric acid component is now considered as an active ingredient by the clinical review team. While the exact mechanism is not known, citric acid appears to increase the sensitivity of the test and allows a smaller dose of $^{13}C$-urea to be administered (75 mg instead of 125 mg). Note that it had been Oridion's contention that the Citrica should be considered a food item since its function is similar to that of other foods, e.g., Ensure pudding, used with urea breath tests.

**C. Basis for Approvability or Not-Approval Recommendation**

This application is now approvable. Deficiencies noted in the original review related to the chemistry, manufacturing and controls of "Citrica," flavored citric acid powder have been adequately addressed. The applicant has reformulated the product; all of the components are of suitable quality for use in this product. A new contract manufacturer of Citrica has been hired. Appropriate manufacturing and packaging conditions have been adequately established and documented. The stability of the product under the proposed storage conditions has been demonstrated.

## III. Administrative

### A. Reviewer's Signature

{see attached electronic signature page}

### B. Endorsement Block

{see attached electronic signature page}

### C. CC Block:

Orig. NDA
HFD-590/Div. File
HFD-590/NSchmuff
HFD-590/MSeggel
HFD-590/JMeyer
HFD-590/SPeacock

22 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

---

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

---

/s/

---

Mark Seggel
12/17/02 10:35:32 AM
CHEMIST
N21-314

Gene Holbert
12/17/02 10:41:52 AM
CHEMIST
For Norman Schmuff

# NDA 21-134

## IDkit:hp™ ($^{13}$C-Urea Tablet)

## Oridion Medical 1987 Ltd.

Mark R. Seggel
Division of Special Pathogen and
Immunologic Drug Products

# Table of Contents

Appears This Way
On Original

# Chemistry Review Data Sheet

1. NDA 21-314

2. REVIEW #: 1

3. REVIEW DATE: 29-NOV-2001

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS: Not Applicable

| Previous Documents | Document Date |
|---|---|
| None | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | February 2, 2001 |
| BL | July 8, 2001 |
| BL | October 10, 2001 |
| BC | October 24, 2001 |
| BC | November 6, 2001 |
| BL | November 12, 2001 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Oridion Medical 1987 Ltd. |
| Address: | 7 Ha Marpe<br>POB 45025<br>Jerusalem 91450 Israel |

Chemistry Review Data Sheet

| | |
|---|---|
| Representative: | Oridion Medical Inc.<br>77 Franklin St.<br>Boston, MA 02110 |
| Telephone: | 617-482-0818 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: IDkit:Hp™ (a component of the BreathID™ System)
b) Non-Proprietary Name (USAN): $^{13}$C-Urea Tablets/Citric Acid
c) Code Name/# (ONDC only): n/a
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50

10. PHARMACOL. CATEGORY: Diagnostic for *H. pylori* infection

11. DOSAGE FORM: Tablet for Oral Solution/Powder for Oral Solution

12. STRENGTH/POTENCY: 75 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OTC

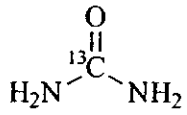
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X__Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$^{13}$C-Urea (99% enriched)
CAS Registry: 58069-82-2
Molecular Formula: $^{13}CH_4N_2O$
Formula Weight: 61.06



## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF# | Type | Holder | Item Referenced | Code | Status | Date Review Completed | Comments |
|---|---|---|---|---|---|---|---|
| [ ] | II | [ | [ $^{13}$C-Urea | 3 | Adequate[a] | 3/3/01 | LoA 8/10/00 |
| [ ] | III | ] | | 4 | N/A | last reviewed 2/16/01 | Contract [ ] LoA 12/13/00 |

[a]Last reviewed March 3, 2001; some deficiencies related to method validation were noted, but the DMF was found adequate to support the manufacture of $^{13}$C-urea (see Chemistry Review of N20-586/SE2-004).

[b]Type I DMF resubmitted as Type III but does not contain specific CMC information. [ ] performs contract [ ] for a very large number of pharmaceutical companies. [ ] has acceptable cGMP status.

**B. Other Documents:** Not Applicable

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | | | |
| EES | acceptable | July 9, 2001 | J. D'Ambrogio |
| Pharm/Tox | | | |
| Biopharm | | | |
| LNC | n/a | | |
| Methods Validation | pending | | |
| OPDRA | comments provided | October 5, 2001 | H.-J. Kim, Pharm.D. |
| EA | n/a | | |
| Microbiology | | | |

# The Chemistry Review for NDA 21-314

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The application is currently deficient with respect to the chemistry, manufacturing and controls for "Citrica," the citric acid-containing component of the IDkit-hp™. From the chemistry perspective it is, therefore, recommended that an Approvable Letter be issued.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is $^{13}$C-labeled urea, 99%-enriched. Carbon-13 is a stable, non-radioactive isotope of carbon that occurs in nature at approximately [ ] Labeled $^{13}$C-urea is currently manufactured by [ ] The chemistry, manufacturing and controls are documented in Type II DMF [ ] Acceptance of the drug substance by the product manufacturer, [ ] is based on the — Certificate of Analysis, along with USP identification tests and identification of carbon-13 by [ ] is an approved supplier of $^{13}$C-urea to Meretek (NDA 20-586).

The drug product consists of a tablet containing 75 mg $^{13}$C-enriched urea and a packet of — flavored citric acid drink mix (Citrica). [ ]

] The tablet is manufactured by — Individual tablets are packaged in [ ] pouches by [ ]. The manufacturing and packaging processes are adequately described. The necessary controls to assure the identity, strength, quality and purity of the $^{13}$C-urea tablet have been established. The stability of the — product has been demonstrated at 25°C/60% RH and 40°C/75% RH, for [ ] respectively. Supporting stability data through [ ] at 25°C/60% RH and [ ] at 40°C/75% were obtained on [ ] development batches of the same formulation. The proposed expiration dating period of [ ] for product stored at 15-30°C is acceptable.

Citrica is composed of citric acid NF (4 g), aspartame, NF [ ], [ ] flavor [ ] and what is referred to as [ ] FD&C Yellow No. 6 [ ] It is packaged in unit-of-use [ ] foil pouches. Citrica is manufactured by [ ]. Both facilities are reported to be in compliance with Israeli food GMPs, however this does not insure adequate control of the manufacturing process or product quality as noted below. It has been Oridion's contention that the Citrica should be considered a food item since its function is similar to that of other foods, e.g., Ensure pudding, used with urea breath tests. The original NDA submission provided little useful information regarding the components of Citrica. At our request, additional information on the ingredients and packaging materials was provided. The applicant has agreed to assure that identification testing is performed on all components. Nevertheless, the use of the proposed dye and flavor present problems. FD&C Yellow No. 6 shall conform in identity and specifications to the requirements of 21 CFR 74.706(a)(1) and (b). Furthermore, FD&C Yellow No. 6 shall be certified in accordance with 21 CFR 80. The documentation from the vendor, [ ] does not assure compliance with these regulations.

The Certificate of Analysis for [ ], again from [ ], states that all ingredients [ ] "are in accordance with the American list of flavoring materials GRAS, FEMA and the FCC III." Without further documentation from either Oridion or [ ] it is impossible to verify the suitability of these components.

The proposed specification does not include a specific identity test for citric acid, although [ ] The HPLC procedure for [ ] assay has not been adequately validated. The proposed — limit for [ ] and — limit for Other Impurities in Citrica suggests extensive decomposition of [ ] The proposed — limit [ ] is also not justified.

Several problems were observed in stability samples of Citrica. The instability of aspartame at elevated temperatures is well known. However, a sample stored at 25°C/60% RH for [ ] was [ ] could not be tested. Other samples at this time point, and subsequently, were found to conform to specification. No explanation was provided and necessary corrective action is not described. The problem suggests that the manufacturing and/or packaging operation is not adequately controlled. Additional problems were observed in samples stored at 30°C/60% RH, [ ] in other impurities. The proposed storage condition, [ ] is inconsistent with these observations.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is used in combination with Oridion's BreathID™ System, a $^{13}C$-urea breath test. This system is primarily a diagnostic device for the detection of gastroduodenal *Helicobater pylori* infection. This device measures the ratio of $^{13}C$-carbon dioxide and $^{12}C$-carbon dioxide exhaled by the patient subsequent to administration of $^{13}C$-urea. Elevated levels of $^{13}CO_2$ are indicative of *H. pylori* urease enzyme activity. The test is performed entirely in a doctor's office. The device is based on isotope-specific infrared spectrometry and what is referred to as "molecular correlation spectrometry." A 510k for the device was recently approved by CDRH. The $^{13}C$-urea tablet and the flavored citric acid powder are dissolved in a glass of water (200 mL) for oral administration at the beginning of the test. The citric acid component is included to delay gastric emptying.

**C. Basis for Approvability or Not-Approval Recommendation**

This application is approvable pending resolution of issues related to the chemistry, manufacturing and controls of "Citrica," flavored citric acid powder. The applicant has not adequately demonstrated that all of the components are of suitable quality for use in this product. Appropriate manufacturing and packaging conditions have not been adequately established and documented. Additional process and quality controls must be established. The stability of the product under the proposed storage conditions has not been demonstrated.

## III. Administrative

**A. Reviewer's Signature**

{see attached electronic signature page}

**B. Endorsement Block**

{see attached electronic signature page}

**C. CC Block:**
Orig. NDA
HFD-590/Div. File
HFD-590/NSchmuff
HFD-590/Mseggel
HFD-590/JMeyer
HFD-590/YKong

40 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

---

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

---

/s/

---

Mark Seggel
1/28/02 04:15:52 PM
CHEMIST
N21314 Chemistry Review#1

Norman Schmuff
1/29/02 09:30:50 AM
CHEMIST

4 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling