

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-137

Administrative/Correspondence

2113

Vintage

Pharmaceuticals, Inc.

odpark Blvd.
e, NC 28206

(704) 596-0516

Vintage certifies that, to the best of its knowledge, there are not active, competitor patents that claim the drug substance, drug product or method of using the drug product that would affect the marketability of the proposed product.

Certification per section 505(b)(2) of the Food, Drug and Cosmetic Act:

In the opinion, and to the best knowledge of Vintage there are no patents that claim the drug on which investigations are relied upon in this application were conducted or that claim a use of such drug or drugs.

rcld
Rebecca Childers
Regulatory Affairs

5/20/99
Date

EXCLUSIVITY SUMMARY for NDA # 21-137 SUPPL # N/A
Trade Name Levolet Generic Name levothyroxine sodium tablets
Applicant Name Vintage Pharmaceuticals Inc. HFD- 510
Approval Date TBD

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 / / NO / /

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

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 / / 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 /_X_/ NO /___/

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 /___/ NO /___/

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

NDA #

NDA #

NDA #

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 /___/ 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 /___/ 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 /___/

- (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 /___/

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 #

Investigation #2, Study #

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 /___/

Investigation #2 YES /___/ NO /___/

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 /___/
Investigation #2 YES /___/ NO /___/
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 #__, Study #
Investigation #__, Study #
Investigation #__, Study #

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 # _____ YES /___/ ! 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 /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____

(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 /___/

If yes, explain: _____

 /s/ 05.22.2003
Prepared by: Enid Galliers
 Chief, Project Management Staff
 DMEDP (HFD-510)

{See appended signature page.}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)

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this page is the manifestation of the electronic signature.**

/s/

David Orloff
5/22/03 07:10:04 PM

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21137</u>	Trade Name:	<u>LEVOLET(LEVOTHYROXINE SODIUM)25/30 MCG T</u>
Supplement Number:		Generic Name:	<u>LEVOTHYROXINE SODIUM</u>
Supplement Type:		Dosage Form:	<u>Tablet, Dispersible; Oral</u>
Regulatory Action:	<u>AE</u>	Proposed Indication:	<u>1. Indicated as replacement or substitution therapy for diminished or absent thyroid function. 2. To suppress endogenous TSH in the treatment of goiter nodules and thyroid cancer.</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

- NeoNates (0-30 Days) Children (25 months-12 Years)
- Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy	<u>Adequate for ALL pediatric age groups</u>
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

No clinical studies were needed. Published literature was provided to support the application.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, STEPHEN MCCORT

Signature *S*

Date 2-23-2000

VINTAGE PHARMACEUTICALS, INC.
Levothyroxine Sodium Tablets, USP

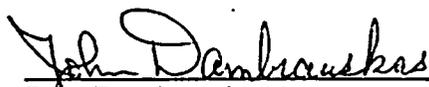
CERTIFICATION PURSUANT TO SECTION 306(k)
OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, AS AMENDED
REGARDING DEBARRED OR CONVICTED PERSONS

Product: Levothyroxine Sodium Tablets, USP

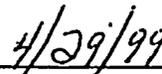
Vintage Pharmaceuticals, Inc. hereby certifies:

1. that we did not use, in any capacity, the services of any person debarred under subsection (a) or (b) of this section in connection with the development or submission of this application;
2. that we will not use in any capacity the services of any person debarred under subsection (a) or (b) of this section in connection with this application; and
3. that neither the applicant nor affiliated persons responsible for the development or submission of this application have been convicted within the past five (5) years of offenses described in subsections (a) and (b) of this section.

Certified
By:



John Dambrauskas
General Manager,
Vintage Pharmaceuticals, Inc.



Date

Division of Metabolic and Endocrine Drug Products
REGULATORY PROJECT MANAGER LABELING REVIEW

Application number: NDA 21-137

Name of Drug: Levolet (Levothyroxine Sodium Tablets, USP)

Applicant: Vintage Pharmaceuticals, Inc.

Material Reviewed:

Submission Date: April 7, 2003, Final Printed Labeling (FPL)

Receipt Date: April 8, 2003

BACKGROUND AND SUMMARY

This NDA was approvable June 12, 2002 pending revised labeling. The firm has submitted FPL.

REVIEW

Package Insert

The FPL (IN-181/8180577, Revised 12/02, R1) was compared to the draft labeling attached to the AE letter. It is identical with the text provided in the labeling attached to the AE letter, and the sponsor has made the product-specific changes requested.

Bottle labels

NOTE: The FPL for the various tablet strengths was compared to the draft labeling issued to the firm with the AE letter. The labels are identical to the draft except that the identifier has been expanded to include "80" at the beginning of the identifier number ("80214" on the draft labels became "8080214" on the FPL) and the revision dated was updated.

-0.025 mg (100 tablets). FPL (8080216 3852, Rev. 1/03 R3)

-0.025 mg (1000 tablets). FPL (8080215 3852, Rev 1/03 R3)

-0.05 mg (100 tablets). FPL (8080214 3853, Rev 1/03 R3)

-0.05 mg (1000 tablets). FPL (8080213 3853, Rev. 1/03 R3)

-0.075 mg (100 tablets). FPL (8080212 3854, Rev 1/03 R3)

-0.075 mg (1000 tablets). FPL (8080211 3854, Rev 1/03 R3)

-0.088 mg (100 tablets). FPL (8080210 3855, Rev 1/03 R3)

-0.088 mg (1000 tablets). FPL (8080209 3855, Rev 1/03 R3)

-0.1 mg (100 tablets). FPL (8080209 3856, Rev 1/03 R3)

-0.1 mg (1000 tablets). FPL (8080207 3856, Rev 1/03 R3)

-0.112 mg (100 tablets). FPL (8080206 3857, Rev 1/03 R3)
-0.012 mg (1000 tablets). FPL (8080205 3857, Rev 1/03 R3)

-0.125 mg (100 tablets). FPL (8080204 3858, Rev 1/03 R3)
-0.125 mg (1000 tablets). FPL (8080203 3858, Rev 1/03 R3)

-0.137 mg (100 tablets). FPL 8080202 3859, Rev 1/03 R3)
-0.137 mg (1000 tablets). FPL (8080201 3859, Rev 1/03 R3)

-0.15 mg (100 tablets). FPL (8080200 3860, Rev 1/03 R3)
-0.15 mg (1000 tablets). FPL (8080199 3860, Rev 1/03 R3)

-0.175 mg (100 tablets). FPL (8080198 3861, Rev 1/03 R3)
-0.175 mg (1000 tablets). FPL (8080197 3861, Rev 1/03 R3)

-0.2 mg (100 tablets). FPL (8080196 3862, Rev 1/03 R3)
-0.2 mg (1000 tablets). FPL (8080195 3862, Rev 1/03 R3)

-0.3 mg (100 tablets). FPL (8080194 3863, Rev 1/03 R3)
-0.3 mg (1000 tablets). FPL (8080193 3863, Rev 1/03 R3)

CONCLUSIONS

The labeling is acceptable. An approval letter should be issued.

Kati Johnson
Chief, Project Management Staff, HFD-510
Labeling Reviewer

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/s/

Kati Johnson
6/5/03 04:31:55 PM
CSO

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6/12/02

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-137	Efficacy Supplement Type SE- (N/A)	Supplement Number (N/A)	
Drug: Levolet (levothyroxine sodium tablets, USP)		Applicant: Vintage Pharmaceuticals	
RPM: E.Galliers		HFD- 510	Phone # 76429
Application Type: () 505(b)(1) (X) 505(b)(2)		NDA 21-301 Reference Listed Drug (NDA #, Drug name): Levoxyl	
❖ Application Classifications:			
• Review priority		(X) Standard () Priority	
• Chem class (NDAs only)		5	
• Other (e.g., orphan, OTC)		N/A	
❖ User Fee Goal Dates RS6 = 18-Jun-2002		AGD = 13-JUN-2002	
❖ 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		(X) Paid	
• User Fee waiver		() Small business () Public health () Barrier-to-Innovation () Other	
• User Fee exception		() Orphan designation () No-fee 505(b)(2) () Other	
❖ 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)			
• OC clearance for approval			
❖ 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		21 CFR 314.50(i)(1)(i)(A) () I () II () III () IV 21 CFR 314.50(i)(1) (x) (ii) () (iii) 20-MAY-1999	
• 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 notice).		() Verified N/A	

Exclusivity (approvals only)		
• Exclusivity summary		NOT NEEDED FOR AE ACTION
• 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)		
General Information		
❖ Actions		
• Proposed action		() AP () TA (X) AE () NA
• Previous actions (specify type and date for each action taken)		AE 3/10/2000; NA= 3/23/2001
• Status of advertising (approvals only)		() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications		
• Press Office notified of action (approval only)		() Yes (X) Not applicable
• 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)		LEVOLET TEMPLATE (6/7/02 ed)
• Most recent applicant-proposed labeling		PI: April 30, 1999 Labels: May 10, 2002
• Original applicant-proposed labeling		April 30, 1999
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)		DMETS:6/7/02; 6/11/02;4/19/02;2/22/00;2/25/00
• Other relevant labeling (e.g., most recent 3 in class, class labeling)		N/A
❖ Labels (immediate container & carton labels)		
• Division proposed (only if generated after latest applicant submission)		X (6/8/02 ed.)
• Applicant proposed	April 30, 1999	Feb.15, 2000; May 10, 2002
• Reviews		June 11, 2002
❖ Post-marketing commitments		
• Agency request for post-marketing commitments		None
• 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)		12.18.1996; 10.01.1998
• Pre-Approval Safety Conference (indicate date; approvals only)		N/A
• Other	Pre-IND - 10.14.1999; Filing - 06.22.1999	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)	YES
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	2/21/00; 3/2/00; 3/23/01; 6/12/02
Clinical Information	
❖ Clinical review(s) (indicate date for each review) 02.19.2000; 07.02.2001 (2); 02.08.2002	X
❖ Microbiology (efficacy) review(s) (indicate date for each review) <i>Finan. Disc.</i>	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	N/N
❖ Statistical review(s) (indicate date for each review) <i>2/19/00</i>	N/A
❖ Biopharmaceutical review(s) (indicate date for each review) <i>3/1/01; 8/8/01; 10/15/01;</i>	4/10/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	2/10/2000
CMC Information	
CMC review(s) (indicate date for each review) <i>2/11/00; 2/18/00; 3/12/01; 2/15/01;</i>	6/7/2002
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	2/11/00
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s)	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable 4/10/02 () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not requested:
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	2/14/00; 7/3/01
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

*** TX REPORT ***

TRANSMISSION OK

TX/RX NO 0298
CONNECTION TEL 917045986237
CONNECTION ID
ST. TIME 06/13 09:54
USAGE T 05'29
PGS. SENT 19
RESULT OK

facsimile

TRANSMITTAL

to: Christopher Nascone
fax #: 704-598-6237
re: AE (approvable) letter for NDA 21-137
date: 13 June 2002
pages: 19 (including cover page)

The package insert that is enclosed with the letter is substantially the same as the one sent on April 18, 2002; however, some typographical errors have been corrected. Please let me know if you want an MSWord copy by email. *S*

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Division of Metabolic and Endocrine Drug Products

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/s/

Enid Galliers

6/12/02 07:38:16 PM

6/1/02

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 5/21/02	DUE DATE: 6/10/02	ODS CONSULT #: 02-0113
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TO:
 David Orloff, M.D.
 Director, Division of Metabolic and Endocrine Drug Products
 HFD-510

THROUGH:

Steve McCort
 Project Manager
 HFD-510

PRODUCT NAME: Levolet (Levothyroxine Sodium Tablets, USP) 25 mcg, 50 mcg, 75 mcg, 88 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg NDA #: 21-137	NDA SPONSOR: Vintage Pharmaceuticals, Inc.
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SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Levolet" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

DMETS does not object to the use of the proprietary name, "Levolet". In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

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 Carol Holquist, R.Ph.
 Deputy Director,
 Division of Medication Errors and Technical Support
 Office of Drug Safety
 Phone: (301) 827-3242 Fax: (301) 443-5161

 Jerry Phillips, R.Ph.
 Associate Director
 Office of Drug Safety
 Center for Drug Evaluation and Research
 Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 30, 2002
NDA NUMBER: 21-137
NAME OF DRUG: Levolet (Levothyroxine Sodium Tablets, USP)
25 mcg, 50 mcg, 75 mcg, 88 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg,
200 mcg, and 300 mcg
NDA HOLDER: Vintage Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for assessment of the tradename "Levolet", regarding potential name confusion with other proprietary/established drug names. In addition, the container labels and insert labeling were provided for review and comment.

Levothyroxine drug products were introduced to the U.S. market before 1962 without an approved New Drug Application (NDA). On August 14, 1997, the FDA announced through the Federal Register Notice (Volume 62, No. 157) that all orally administered levothyroxine sodium drug products are new drugs and, therefore, are subject to an approved NDA after August 14, 2000. Currently, *Unithroid* (approved August 21, 2000), *Levoxyl* (approved May 25, 2001), and *Levo-T* (approved March 1, 2002) are approved for the U.S. market.

PRODUCT INFORMATION

Levolet is the proposed proprietary name for levothyroxine sodium tablets. It is a synthetic formulation of tetraiodothyronine sodium (T_4) and is considered a narrow therapeutic index drug. Levolet is indicated for use as replacement or supplemental therapy in patients with hypothyroidism, except in cases of transient hypothyroid states during the recovery phase of subacute thyroiditis. The drug is also indicated for use as a pituitary TSH suppressant in the treatment or prevention of various euthyroid goiters including thyroid nodules, subacute and chronic lymphocytic thyroiditis (Hashimoto's) and multinodular goiter. Additional indications include use in conjunction with surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid. This drug product is contraindicated in patients with untreated thyrotoxicosis and uncorrected adrenal insufficiency. The recommended dose for adults and children whose growth and puberty are complete is approximately 1.7 mcg/kg/day (100-125 mcg/day for a 70 kg adult). The dose should be taken in the morning on an empty stomach. Elderly patients may require less than

1 mcg/kg/day. The recommended dose for pediatric hypothyroidism will vary with age and weight. Levolet will be available as a 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg tablet.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound alike or look alike to "Levolet" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the data provided by Thomson & Thomson's SAEGIS™ Online Service⁴ was also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies of each proposed proprietary name consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

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

1. Five product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Levolet. These products are listed in Table 1 (page 4) along with the dosage forms available and usual FDA-approved dosage.
2. DDMAC had no concerns with "Levolet" with regard to promotional claims.

**APPEARS THIS WAY
ON ORIGINAL**

¹ MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfit K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2001).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ The Established Evaluation System [EES], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.thomson-thomson.com>.

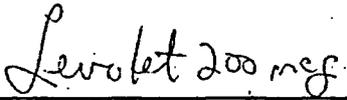
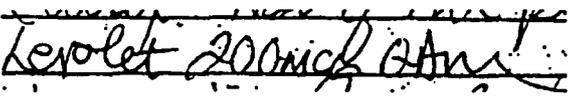
Table 1

Product Name	Dosage form(s)	Generic name	Usual adult dose	Other
Levolet	Levothyroxine Sodium Tablets, USP 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg (Rx)	Levothyroxine Sodium Tablets, USP	100 mcg - 125 mcg/day (range: 12.5 mcg - 300 mcg/day per patient response)	
Levlite	Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1mg/0.03mg (Rx) 21 and 28 day packs	Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1mg/0.03mg (Rx)	1 tablet once daily	*SA/LA
Levophed	Norepinephrine 1 mg/mL (4 mL ampules) (Rx)	Norepinephrine 1 mg/mL (4 mL ampules) (Rx)	0.5 to 1 mL per minute given IV	*S/A
Levatol	Penbutolol Sulfate Tablets 20 mg	Penbutolol Sulfate Tablets 20 mg	1 tablet once daily	*LA
Levulan Kerastick	Aminolevulinic Acid Topical Solution 20% (Rx)	Aminolevulinic Acid Topical Solution 20% (Rx)	One application of solution with one dose of illumination per treatment site per 8-week treatment session	*SA/LA
Levlen	Levonorgestrel and Ethinyl Estradiol Tablets 0.15 mg/0.03 mg (Rx) 21 and 28 day packs	Levonorgestrel and Ethinyl Estradiol Tablets 0.15 mg/0.03 mg (Rx)	1 tablet once daily	*S/A, L/A
*Frequently used, not all-inclusive. **SA (sound-alike), LA (look-alike)				

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

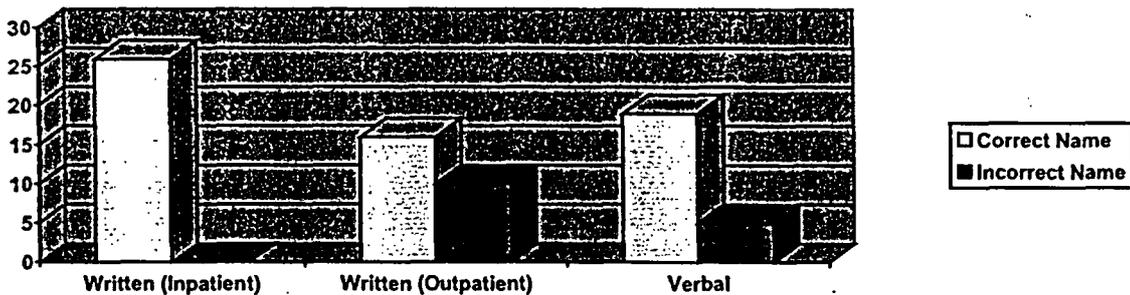
Three studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Levolet with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the name. These studies employed 108 health care professionals comprised of pharmacists, physicians, and nurses. This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and a prescription for Levolet (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a random sample of the participating health care professionals via telephone voicemail. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient Rx: 	Levolet, take 1 tablet daily, dispense #30
Inpatient Rx: 	

2. Results:

Results of the exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Levolet"	Incorrectly Interpreted
Written Inpatient	33	26 (79%)	26 (100%)	0 (27%)
Written Outpatient	39	26 (67%)	16 (62%)	10 (38%)
Verbal Outpatient	36	24 (67%)	19 (79%)	5 (21%)
Total	108	76 (70%)	61 (80%)	15 (20%)



Among the written inpatient prescriptions, 26 of 26 (100%) respondents interpreted "Levolet" correctly.

Among the written outpatient prescriptions, 10 of 26 (38%) respondents interpreted "Levolet" incorrectly. The majority of the incorrect interpretations were misspelled variations to the name Levolet. Interpretations included *Levofet* (7), *Levobet* (2), and *Levotet*.

Among the verbal outpatient prescriptions, 5 of 24 (21%) respondents interpreted "Levolet" incorrectly. Interpretations included *Levolette*, *Levolet*, *Levolet*, *Levoled*, and *Lovolet*.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Levolet", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for confusion include *Levlen*, *Levlite*, *Levulan*, *Levophed*, and *Levatol*.

Levlen is a monophasic oral contraceptive that contains 0.15 mg of levonorgesterol and 0.03 mg of ethinyl estradiol. *Levlen* is indicated for the prevention of pregnancy in women. *Levlen* and *Levolet* can look and sound somewhat similar. The first six letters in *Levolet* look very similar to the first five letters in *Levlen*. Both drug products also share a once daily dosing regimen. However, *Levolet* will be available in multiple strengths and will require a strength for dispensing. *Levlen*, on the other hand, is available in one strength but in packs of 21 and 28 tablets. A prescription written for "*Levlen-21*" or "*Levlen-28*" will also be distinguishable since the numerals 21 and 28 do not overlap with the proposed *Levolet* strengths. In addition, a prescription for *Levlen* will most likely include unit quantities of 1, 2, or 3 whereas *Levolet* will include larger quantities of 30, 60, or 90. Furthermore, the unique packaging configuration will aid in preventing the error from occurring.

Levlite is an oral contraceptive that contains 0.1 mg of levonorgesterol and 0.03 mg of ethinyl estradiol. *Levlite* is indicated for the prevention of pregnancy in women. *Levlite* and *Levolet* look and sound similar when scripted (see writing sample below). Both drug products share a once daily dosing regimen. However, *Levolet* will be available in multiple strengths and will require a strength for dispensing. *Levlite*, on the other hand, is available in one strength but in packs of 21 and 28 tablets. A prescription written for "*Levlite-21*" or "*Levlite-28*" will also be distinguishable since the numerals 21 and 28 do not overlap with the proposed *Levolet* strengths. In addition, a prescription for *Levlite* will most likely include unit quantities of 1, 2, or 3 whereas *Levolet* will include larger quantities of 30, 60, or 90. Furthermore, the unique packaging configuration will aid in preventing the error from occurring.



Levulan Kerastick (Aminolevulinic Acid) for topical solution is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face or scalp used in conjunction with a blue light illumination therapy. *Levulan* is applied once per treatment site during an 8-week treatment period. In addition, *Levulan* is restricted for use by a qualified health care professional. Although *Levulan* and *Levolet* may look and sound similar, the risk of confusion between the two products is low based on differences in dosage form, dosing regimen, restrictions for use by qualified professionals, and indication.

Levophed the proprietary name for norepinephrine bitartrate and is indicated for blood pressure control in certain acute hypotensive states (e.g., pheochromocytectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions). It is also indicated as an adjunct in the treatment of cardiac arrest and profound hypotension. *Levophed* is supplied as a sterile aqueous solution of 1 mg/mL (4 mL ampule) in the form of the bitartrate salt to be administered by intravenous infusion following dilution. The recommended dose of *Levophed* is 0.5 to 1 mL per minute given IV. *Levophed* and *Levolet* may

sound similar when pronounced. However, the drug products differ in dosage form, dosing regimen, strength, and indication for use. Therefore, the risk of confusion is low based on the aforementioned differences.

Levatol contains penbutolol sulfate and is indicated in the treatment of mild to moderate arterial hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. Levatol is available as a 20 mg tablet. The recommended dose is 20 mg once daily. Levatol and Levolet look similar when scripted, varying in the last 4 letters of the name (see writing sample below). Furthermore, Levatol and Levolet share a once daily dosing regimen and dosage form. However, the drug products differ in strength. Although the products share similar numerical strengths (200 mcg vs. 20 mg), a prescription for Levolet will be prescribed with a strength, whereas Levatol may be prescribed without a strength since it is available in only one strength. Therefore, the risk of confusion between Levatol and Levolet is minimal.

Levatol Levolet

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the draft carton label and insert labeling for Levolet, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified areas of possible improvement, which might minimize potential user error.

CONTAINER LABELS

1. [

J

2. The tablet strengths from 0.88 mg and higher have less prominence than the net quantity. Increase the prominence of the strength so that it appears more prominent than the net quantity.

III. RECOMMENDATIONS:

- A. DMETS does object the use of the proprietary name "Levolet".
- B. DMETS recommends implementation of the labeling revisions outlined in section III that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names from the signature date of this document.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

|S|

Alina R. Mahmud, RPh.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Alina Mahmud
6/6/02 10:35:59 AM
PHARMACIST

Carol Holquist
6/7/02 03:47:43 PM
PHARMACIST

Jerry Phillips
6/7/02 03:55:46 PM
DIRECTOR

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6/10/02

Division of METABOLIC AND ENDOCRINE DRUG PRODUCTS
CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 21-137

Name of Drug: Levolet (levothyroxine sodium tablets, USP),
0.025, 0.05, 0.075, 0.088, 0.1, 0.112, 0.125, 0.137, 0.15, 0.175, 0.2, 0.3 mg.

Sponsor: Vintage Pharmaceuticals, Inc.

Material Reviewed:

Submission Date(s): Package insert: April 30, 1999; Labels: May 10, 2002

Receipt Date(s): Package insert: May 3, 1999; Labels: May 13, 2002

Background and Summary

The firm proposed the proprietary name "Levolet," and ODS/DMETS and DMEDP found it acceptable.

A package insert was submitted in the original submission (April 30, 1999). The Agency told the firm that the presence of potassium iodide in the product necessitated modifications in the levothyroxine sodium tablets package insert template, and the Agency would supply the modified template to the firm.

The Agency requested changes to the labels and labeling in an April 18, 2002, Information Request (IR) letter. The IR letter included a levothyroxine sodium tablets package insert template modified for this product. On May 10, 2002, the firm submitted revised bottle labels for 100-ct and 1000-ct bottles for all strengths. The firm did not include a package insert in that submission - stating that it did not agree with some of the warning language in the template.

Review

The NDA does not contain a satisfactory package insert.

The bottle labels are described in the following chart. They comply with the requirements at 21 CFR 201.57 and have incorporated the changes requested by the Agency. However, the labels are all printed in green ink on a gray background and use various geometric shapes around each strength to differentiate among the 12 strengths. DMETS/ODS has suggested that using a color that matches the contents of the bottle to differentiate strengths might avoid dispensing errors.

DMETS also commented that the net quantity appeared to be more prominent than the tablet strength on the labels for 0.088 mg and larger strength bottles. The review chemist agrees with both suggestions, but does not consider them approvability issues. Therefore, these comments will be added to the approvable (AE) letter as suggestions.

Tablet Strength mg	Background Shape	Identifier #	
		100-ct bottle	1000-ct bottle
0.025	None	80216 3852 Rev. 4/02 R2	80215 3852 Rev. 4/02 R2
0.05	Hollow rectangle	80214 3853 Rev. 4/02 R2	80213 3853 Rev. 4/02 R2
0.075	Solid rectangle	80212 3854 Rev. 4/02 R2	80211 3854 Rev. 4/02 R2
0.088	Hollow oval	80210 3855 Rev. 4/02 R2	80209 3855 Rev. 4/02 R2
0.1	Solid oval	80208 3856 Rev. 4/02 R2	80207 3856 Rev. 4/02 R2
0.112	Hollow diamond	80206 3857 Rev. 4/02 R2	80205 3857 Rev. 4/02 R2
0.125	Solid diamond	80204 3858 Rev. 4/02 R2	80203 3858 Rev. 4/02 R2
0.137	Hollow octagon /	80202 3859 Rev. 4/02 R2	80201 3859 Rev. 4/02 R2
0.15	Solid octagon /	80200 3860 Rev. 4/02 R2	80199 3860 Rev. 4/02 R2
0.175	Hollow circle	80198 3861 Rev. 4/02 R2	80197 3861 Rev. 4/02 R2
0.2	Solid circle	80196 3862 Rev. 4/02 R2	80195 3862 Rev. 4/02 R2
0.3	Hollow triangle	80194 3863 Rev. 4/02 R2	80193 3863 Rev. 4/02 R2

Conclusions

The container labels are satisfactory, but suggestions (rather than requirements) for color-coding the strength and reducing the prominence of the net quantity will be included in the action letter. The product cannot be approved until an acceptable package insert is submitted.

{See appended electronic signature}

Enid Galliers
Chief, Project Management Staff

Supervisory Comment/Concurrence:

{See appended electronic signature}

Mary H. Parks, M.D.
Medical Team Leader

NDA 21-137 Levolet
Page 3

Drafted: emg/06.07,10.2002/
Finalized:
Filename: c:\21137\pmlblrev.labels.doc

CSO LABELING REVIEW

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/s/

Enid Galliers
6/10/02 10:13:17 PM
CSO

Mary Parks
6/11/02 08:18:48 AM
MEDICAL OFFICER

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Number of Pages
Redacted 58



Draft Labeling
(not releasable)

facsimile

TRANSMITTAL

to: Christopher Nascone
fax #: 704-598-6237
re: AE (approvable) letter for NDA 21-137
date: 13 June 2002
pages: 19 (including cover page)

The package insert that is enclosed with the letter is substantially the same as the one sent on April 18, 2002; however, some typographical errors have been corrected. Please let me know if you want an MSWord copy by email. Enid Galliers

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Division of Metabolic and Endocrine Drug Products

From the desk of...
Enid Galliers
Chief, Project Management Staff (HFD-510)
DMEDP, ODE II, CDER, FDA
5600 Fishers Lane, Rm 14B-19
Rockville, MD 20857

301-827-6429
Fax: 301-443-9282



An OPTRA consult for Levlet was sent on March 6, 2001. The response to the consult has not been received and is not likely to be received before the Action letter to NDA 21-137 is sent.

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A Financial disclosure statement was not provided. A Financial disclosure statement will be requested in the action letter to the sponsor.

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MEMORANDUM OF TELEPHONE MEETING

MEETING DATE: 30-MAY 2002

TIME: 9:15 AM – 9:27 AM

LOCATION: PKLN 14B-45 C/R

APPLICATION: NDA 21-137 Levolet (levothyroxine sodium tablets) 12 strengths

TYPE OF MEETING: OTHER - FDA request for changes and information

MEETING CHAIR: Steven Johnson, Pharm.D.

MEETING RECORDER: Enid Galliers

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Steven Johnson, Pharm.D.	Biopharmaceutics Reviewer	DPE II, OCPB, OPS, CDER @ DMEDP
2. Sheldon Markofsky, Ph.D.	Acting Team Leader, Chemistry Team II	DNDC II, ONDC, OPS, CDER @ DMEDP
3. David Lewis, Ph.D.	Chemistry Reviewer	DNDC II, ONDC, OPS, CDER @ DMEDP
4. Enid Galliers	CPMS	Div. of Metabolic and Endocrine Products, OND, CDER

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Christopher Nascone	Regulatory Affairs	Vintage Pharmaceuticals, Inc.
2. Pam Troxler		Vintage
3. Fran Hutchins		Vintage

BACKGROUND: Some additional biopharmaceutics and chemistry information is needed before an action letter can issue for Levolet. The user fee goal for Levolet is June 18, 2002, but the planned action date is no later than June 13 (due to the absence of several personnel.)

MEETING OBJECTIVES:

1. The biopharmaceutics reviewer needs to have the firm confirm its current dissolution method and tolerances (acceptance criteria).
2. The chemistry reviewer needs to have the firm describe the HPLC analytical method for determining the contents of the dissolution.
3. The regulatory dissolution methods for release and stability need to be designated.

DISCUSSION POINTS:

1. The firm said that the current dissolution method is a modified one; Apparatus 2 (paddles) @ 75 RPM in _____ in 500 mL. The tolerance (acceptance criterion) is NLT — % (Q) @ 45 min.
2. FDA indicated that the most recent data submitted by the firm using the modified method support a tolerance of — % (Q) @ 45 min.
3. FDA learned that the _____ method is by the current USP HPLC method.
4. FDA asked the firm what they intend to use as the regulatory stability method and commented that the firm could use its modified method as the alternate method and the USP method as the regulatory method. The alternate method can be used routinely
5. FDA commented that we still need to determine if this is a "USP" product because it does not exactly follow the USP method.

DECISIONS (AGREEMENTS) REACHED:

1. Vintage agreed to the FDA-established tolerance specification and will incorporate it in their methods.
2. Vintage agreed to correct its stability method and specifications to include reference to the method by the method number and a statement describing its relationship to the relevant USP issuance.

3. Vintage will designate the current USP dissolution method as the regulatory method for release and utilize their in-house method (Apparatus 2, paddles @ 75 rpm in _____ as the alternate dissolution method.
4. The alternate dissolution method for release will be the regulatory dissolution method for stability.
- 5. The firm will amend the methods and acceptance criteria for all strengths as discussed and will submit them as an amendment to the NDA.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION: None

ACTION ITEMS:

<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>
Submit revised methods and specifications to the NDA.	Vintage Pharmaceuticals	June 4, 2002

{See appendix 1 electronic signature}
Minutes Preparer: _____
Enid Galliers, CPMS, DMEDP

{See appendix 1 electronic signature}
Chair Concurrence: _____
Steven Johnson, Pharm.D.

ATTACHMENTS/HANDOUTS:
None

Drafted by: EMG/06.08.02
Initialed by: S.JOHNSON/06.11.02/ D.LEWIS/06.10.02 (FOR HIMSELF & S.MARKOFSKY)
final: EMG/06.11.2002/ (C:\21137\053002T.CON-BPH.DOC)

MEETING MINUTES

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/s/

Enid Galliers
6/11/02 09:33:37 AM
CSO

Steve Johnson
6/12/02 10:17:39 AM
BIOPHARMACEUTICS

**APPEARS THIS WAY
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: March 20, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA # 21,137
Levolet (levothyroxine sodium) tablets
Vintage Pharmaceuticals, Inc.

SUBJECT: NDA review issues and action related to complete response to AE letter dated March 10, 2000

Background

The NDA for this levothyroxine-containing drug product was originally submitted on April 30, 1999 in response to the Federal Register notice of August 14, 1997 announcing FDA's position that such products are new drugs and must be marketed under approved NDAs. The original review of the application raised clinical safety issues in pregnant and nursing mothers and in neonates related to the inclusion of iodide in the formulation as a stabilizing agent, which were deemed manageable through labeling. These issues are summarized in Dr. Temeck's original medical officer review and in my Team Leader review contained in this package.

On March 10, 2000, the Division issues an approvable letter citing CMC, Biopharmaceutics, and labeling deficiencies. Specifically, with regard to CMC, additional stability data were needed to formulate an acceptable stability bracket for the product; monitoring for degradation products was required; recalculation of the quantitative components and composition of the tablets was required, and an Environmental Impact Report was required.

The Biopharmaceutics deficiencies addressed the absence of dissolution data on the full range of tablet strengths intended for marketing.

Finally, preliminary labeling comments were included in the letter.

The sponsor responded to the AE letter in submissions dated September 25, October 17, and December 19, 2000. The September 25, 2000 submission was considered a complete response, and the 6-month review clock was started. The submissions have been reviewed by OCPB and ONDC, and the findings are summarized below. In addition, the inspection of the manufacturing facility in Charlotte, NC in November 2000 prompted a "Withhold approval" recommendation from the Office of Compliance. Finally, review of the original application revealed that no financial disclosure information had been submitted. This, then, will be addressed in the current letter.

NDA # 21-137
Drug: Levolet (levothyroxine) Vintage
Proposal: approval for marketing, response to AE letter
03/20/01

Medical

No new clinical safety or efficacy issues have been raised.

Labeling

The levothyroxine "template" labeling developed by the Division will be conveyed to the sponsor.

Biopharmaceutics

Dr. Johnson's review of the additional dissolution data submitted supports his conclusion that the dissolution method (USP 23) is not appropriate for this product since it does not permit adequate discrimination in dissolution profiles to be useful as a quality control method. Furthermore, the data therefore do not permit us to grant a waiver of the requirement for bioavailability studies using strengths intermediate to those previously characterized in PK studies. As such, the sponsor needs to develop a discriminating dissolution method appropriate to this product.

Pharmacology/Toxicology

No new issues.

Chemistry/ Manufacturing

As above, the inspection of the manufacturing plant revealed CGMP deficiencies that cause the drug to be adulterated within the meaning of Section 501(a)(2)(B). Indeed, the Office of Compliance has recommended that the Agency invoke the shutdown provision in a 1998 Consent Decree signed by Vintage. The recommendation to the Division is to withhold approval until the CGMP deficiencies have been corrected.

Financial disclosure

As above, no financial disclosure was ever submitted to this application. The in vivo bioavailability studies are considered "covered" studies, and financial disclosure information is therefore required under 21 CFR 54.

OPDRA/nomenclature

A consult on the name "Levolet" is pending from OPDRA.

Recommendation

This NDA should not be approved at this time, pending correction of the deficiencies addressed above.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 25 February 2000

FROM: Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II, CDER

SUBJECT: Financial Disclosure Requirement for NDA 21-137 Levolet (levothyroxine sodium) Tablets

TO: File for NDA 21-137

Upon discussion with Linda Carter, Regulatory Policy Advisor, CDER, it was determined that financial disclosure reporting is not required because neither the literature reports or the pharmacokinetics studies that support this application are considered to be "covered clinical studies" under the financial disclosure reporting rule. Therefore, this application is not subject to the requirement for financial disclosure reporting.

Cc: Orig. NDA 21-137
HFD-510/Div. Files
HFD-510/SMcCort
HFD-501/LCarter

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DATE: March 2, 2000

TO: NDA 21-137

FROM: John K. Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products,
HFD-510

SUBJECT: Overview of NDA Review Issues

IST 3/2/00

Administrative

NDA 21-137 for Levolet (levothyroxine sodium) tablets was submitted by Vintage Pharmaceuticals on May 10, 1999.

This NDA was submitted in response to the Federal Register Notice of August 14, 1997, that announced that orally administered drug products containing levothyroxine sodium are new drugs. This FRN was in response to new information showing significant stability and potency problems with orally administered levothyroxine drug products that are currently marketed in the U.S. as pre-1938 drugs without approved NDAs. The FRN stated that:

“the active ingredient levothyroxine sodium is effective in treating hypothyroidism and is safe when carefully and consistently manufactured and stored, and prescribed in the correct amount to replace the deficiency of thyroid hormone in a particular patient. However, no currently marketed orally administered levothyroxine product has been shown to demonstrate consistent potency and stability, and thus, no currently marketed orally administered levothyroxine sodium product is generally recognized as safe and effective. Accordingly, any orally administered drug product containing levothyroxine sodium is a new drug.....and is subject to section 505 of the act. Manufacturers who wish to continue to market orally administered levothyroxine sodium products must submit applications as required by section 505 of the act and part 314 (21 CFR part 314).” The FRN further stated that “levothyroxine sodium products are medically necessary because they are used to treat hypothyroidism and no alternative drug is relied on by the medical community as an adequate substitute. Accordingly, FDA will permit orally administered levothyroxine products to be marketed without approved NDA’s until August 14, 2000, in order to give manufacturers time to conduct the required studies and to prepare and submit applications, and to allow time for review of and action on the applications.”

The application for Levolet Tablets was assigned a standard review timeline and the 10 month user fee goal date is March 10, 2000.

Clinical

As noted in the FRN, the drug substance levothyroxine sodium is effective in treating

hypothyroidism and is safe when carefully and consistently manufactured and stored, and prescribed in the correct amount to replace the deficiency of thyroid hormone in an individual patient. The sponsor did not submit any new clinical trial data in support of the proposed indication for Levolet tablets. Please refer to the Medical Officer review prepared by Dr. Temeck and the Medical Team Leader memorandum prepared by Dr. Orloff for further details of the review of the available published literature in support of the proposed indications for this drug. I concur with Drs. Temeck and Orloff that there are adequate data to support the safety and efficacy of Levolet for the indications as proposed in Dr. Temeck's review.

An important safety aspect of this application is the inclusion of potassium iodide (KI) as _____ in the Levolet formulation. As outlined by Drs. Temek and Orloff, the KI contained in the Levolet tablet is not a significant safety concern for most patients since it will be administered in combination with levothyroxine sodium. The KI does raise potential safety concerns for the fetus and nursing infants of mothers being treated with Levolet and for patients at risk for iodide-induced thyrotoxicosis (a rare condition in the U.S.). While not a significant safety concern, the KI in Levolet also raises issues of inadequate thyroidal uptake of radioiodine for diagnostic or therapeutic purposes. I concur with Dr. Temeck and Orloff that these issues can adequately be addressed in the labeling for Levolet; in particular the Warnings Section of the labeling will need to reflect the potential risk to the fetus and nursing infant.

This application is approvable from a clinical perspective pending agreement on adequate labeling and pending resolution of the deficiencies noted by other disciplines (see below). Preliminary labeling comments will be forwarded to the sponsor in the action letter.

Pharmacology/Toxicology

The sponsor did not submit any new pharmacology/toxicology data in this application and none were required given the long history of marketing of levothyroxine containing products in the U.S. and the fact that the drug is used as replacement therapy of endogenous thyroid hormone (i.e., the active drug substance in Levolet is chemically identical to the levothyroxine produced naturally in the body). Please refer to the review prepared by Dr. Steigerwalt for an evaluation of the impact of the KI in Levolet tablets on the safety of the drug: Dr. Steigerwalt initially recommended Pregnancy Category _____ for this application. On further internal discussion of the data available for KI from published literature, it was concluded that the Pregnancy Category for Levolet should be ' ____ This conclusion was based on a report of transient hypothyroidism in an infant whose mother received KI in daily doses similar to those in Levolet during pregnancy.

This application is approvable from a pharmacology/toxicology perspective pending agreement on adequate labeling. Preliminary labeling comments, including the need to rewrite the Pregnancy Category Section to reflect a ____ rating will be included in the action letter.

CMC

As noted in the FRN, the primary concern associated with orally administered levothyroxine drug products is potency and stability. Please refer to the CMC review prepared by Dr. Lewis

for this application for details of the chemistry, manufacturing, and controls data submitted in support of this application. The sponsor has not submitted adequate long-term and accelerated stability data under the proper ICH storage conditions to allow an evaluation of the stability of the drug and determination of an acceptable expiry date. The sponsor will need to generate additional stability data as outlined in Dr. Lewis' review (note that the sponsor is being allowed to conduct a "bracketing" stability program given the multiple strengths of Levolet proposed for marketing and the similarity of the formulations of the various strength tablets) and submit these data for review prior to approval.

This NDA is approvable from a CMC standpoint pending the submission of additional stability data collected under proper ICH storage conditions for review. The required data will be requested in the action letter.

Clinical Pharmacology/Biopharmaceutics

To help guide sponsors of NDAs for levothyroxine products, the FDA published a Draft Guidance that outlined the types of bioavailability studies that would be required to support NDA approval. The Guidance recommended a relative bioavailability study comparing the tablet formulation with an equivalent dose of an oral solution. The Guidance also recommended a comparative bioavailability study of low, middle, and high strength tablets in a "bracketing" approach to establish linearity (dose proportionality) between strengths. Finally, the Guidance recommended submission of in-vitro dissolution data using a discriminating method on three production size lots of each to-be-marketed tablet strength. Please refer to the review prepared by Dr. Johnson. The data provided by the sponsor have adequately established the bioequivalence of Levolet to an oral solution and linearity of the different tablet strengths; however, the sponsor did not provide dissolution data on three lots of tablets for each to-be-marketed strength of tablet and did not provide dissolution data on all the tablet lots used in the in-vivo studies. These data will need to be provided and reviewed before this application can be approved.

This NDA is approvable from a Clinical Pharmacology/Biopharmaceutics perspective pending submission and review of additional in-vitro dissolution data. The required data will be requested in the action letter.

DSI

Audits were completed by the Division of Scientific Investigations of the clinical site where the in-vivo bioavailability studies were performed. The audit determined that certain samples for assay of T3 should not be relied on in the review of this application due to concerns regarding the stability of the samples. The data for the levothyroxine levels was not affected by this recommendation and the T3 data are not considered critical to the evaluation of the data by Dr. Johnson.

Labeling

Since no new clinical or preclinical studies were submitted in support of this application, nor

are they expected to be submitted in support of any of the incoming applications for orally administered levothyroxine drug products, the division plans to utilize a "class labeling" approach for these drugs. This class labeling is still under discussion at this time. The sponsor will be provided preliminary comments on their proposed draft labeling in the action letter with further comments to follow when the other deficiencies noted in this letter are adequately addressed and the application is nearing approval. The proposed tradename "Levolet" is acceptable to the Division; however, a consult for the tradename has not been completed by OPDRA at this time. This should not hold up the issuance of an action letter since the tradename review will need to be revisited prior to approval and this application. It is likely that this application will not be approved for up to a year from the upcoming action date due to the need for the sponsor to generate significant amounts of new data and the need for those data to be submitted and reviewed.

Recommendations:

This application cannot be approved at this time due to outstanding deficiencies as outlined above. The sponsor should receive an APPROVABLE letter since the drug product is considered to be safe and effective provided the labeling is successfully negotiated with the sponsor and the outstanding deficiencies appear to be ones that can be addressed adequately with the generation of additional data. The sponsor will be given preliminary labeling comments in the action letter.

CC:

NDA 21-137
HFD-510 Division File
HFD-510/Jenkins
HFD-510/Orloff

**APPEARS THIS WAY
ON ORIGINAL**

The Firm submitted a claim for categorical exclusion and their request was granted.

APPEARS THIS WAY
ON ORIGINAL

Microbiology Review not needed.

APPEARS THIS WAY
ON ORIGINAL

Advisory meeting was not held.

APPEARS THIS WAY
ON ORIGINAL

Div

MEMORANDUM OF TELECON

DATE: March 10, 2000

APPLICATION NUMBER: NDA 21-137; Levolet

BETWEEN:

Name: Chris Nascone
Phone: 256-859-2222
Representing: Vintage Pharmaceuticals

AND

Name: Steve McCort
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Confirmation of receipt of Approvable letter

Letter received by sponsor by FAX.

/S/

Steve McCort
Project Manager, HFD-510

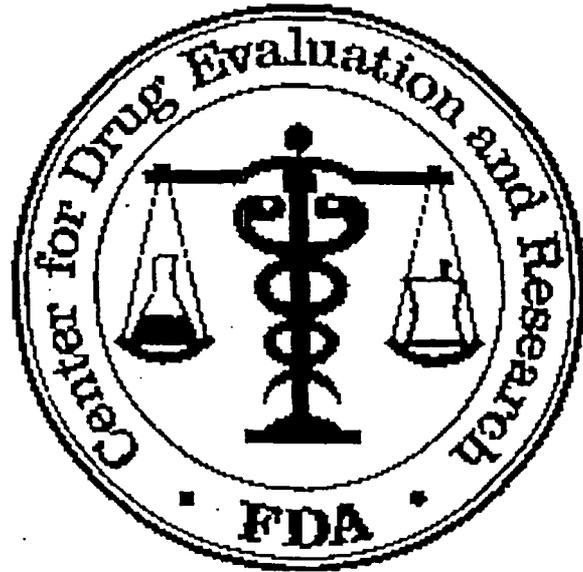
cc: Original NDA 21-137
HFD-510/Div. File
HFD-510/Steve McCort

TELECON

**APPEARS THIS WAY
ON ORIGINAL**

FOOD AND DRUG ADMINISTRATION
DIVISIONS OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: March 10, 2000



TO:

Name:

CHRIS NASCONE

~~Fax~~ No: 256-859-2222

~~Phone~~ No: 256-858-0025

Location: VINTAGE PHARM

FROM:

Name: Steve McCort

Fax No: 301-443-9282

Phone No: 301-827-6415

Location: FDA, Division of
Metabolic and Endocrine
Drug Products, HFD-510

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Comments:

APPROVABLE LETTER (AE) FOR NDA 21-137; LEVOLET



**OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST**

NDA # 21-137 Drug Levolet (levothyroxine sodium) Tablets DATE 2-23-00

Applicant Vintage Pharmaceuticals
CSO McCort /Phone 827-6415

User Fee Goal Date: 3-10-00

Arrange package in the following order:

Check or Comment

- | | |
|---|--|
| 1. ACTION LETTER with supervisory signatures
Are there any Phase 4 commitments? | AP <u> </u> AE <u>X</u> NA <u> </u>
Yes <u>X</u> No <u> </u> |
| 2. Have all disciplines completed their reviews?
If no, what review(s) is/are still pending? | Yes <u>X</u> No <u> </u> |
| 3. Completed copy of this CHECKLIST in package | Chem/Ther Types <u>5S</u> |
| 4. LABELING (package insert <u>and</u> carton and container labels).
(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.) | Draft <u>X</u>
Revised Draft <u> </u>
Final <u> </u> |
| 5. PATENT INFORMATION | <u> </u> X <u> </u>
not needed |
| 6. EXCLUSIVITY CHECKLIST | <u> </u> X <u> </u> |
| 7. PEDIATRIC PAGE | <u> </u> X <u> </u> |
| 8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). | <u> </u> X <u> </u> |
| 9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
If no audits were requested, include a memo explaining why. | <u> </u> AP <u> </u> |
| 10. REVIEWS: | <u> </u> X <u> </u> |
| DIVISION DIRECTOR'S MEMO If more than 1 review for any | <u> </u> X <u> </u> |
| GROUP LEADER'S MEMO 1 discipline, separate reviews | <u> </u> X <u> </u> |
| MEDICAL REVIEW with a sheet of colored paper. | <u> </u> X <u> </u> |
| SAFETY UPDATE REVIEW Any conflicts between reviews | <u> </u> NA <u> </u> |
| STATISTICAL REVIEW must have resolution documented | <u> </u> NOT NEEDED <u> </u> |
| BIOPHARMACEUTICS REVIEW | <u> </u> X <u> </u> |
| PHARMACOLOGY REVIEW (Include pertinent IND reviews) | <u> </u> X <u> </u> |
| Statistical Review of Carcinogenicity Study(ies) | <u> </u> <u> </u> |
| CAC Report/Minutes | <u> </u> <u> </u> |
| CHEMISTRY REVIEW | <u> </u> X <u> </u> |
| Labeling and Nomenclature Committee Review Memorandum | <u> </u> <u> </u> |
| Date EER completed <u>1-09-00</u> (attach signed form or CIRTS printout) | <u> </u> Review pending <u> </u> |
| No <u> </u> FUR needed <u> </u> FUR requested <u> </u> | <u> </u> OK <u>X</u> <u> </u> |
| Have the methods been validated? | Yes (attach) <u> </u> No <u>X</u> <u> </u> |
| Environmental Assessment Review / FONSI (EA not submitted
By Sponsor | <u> </u> <u> </u> |
| Review <u>no</u> FONSI no <u> </u> | <u> </u> NA <u> </u> |
| MICROBIOLOGY REVIEW | <u> </u> <u> </u> |
| What is the status of the monograph? | <u> </u> <u> </u> |
| 11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes | <u> </u> X <u> </u> |
| 12. MINUTES OF MEETINGS | <u> </u> X <u> </u> |
| Date of End-of-Phase 2 Meeting <u> </u> | <u> </u> <u> </u> |
| Date of pre-NDA Meeting <u>10-1-98</u> | <u> </u> <u> </u> |
| 13. ADVISORY COMMITTEE MEETING MINUTES
or, if not available, 48-Hour Info Alert or pertinent section of transcript. | Minutes <u> </u> Info Alert <u> </u>
Transcript <u> </u> No mtg <u>X</u> <u> </u> |
| 14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS | <u> </u> X <u> </u> |
| 15. If approval letter, has ADVERTISING MATERIAL been reviewed?
If no and this is an AP with draft labeling letter, has
advertising material already been requested? | Yes <u> </u> No <u>X</u> <u> </u>
Yes, documentation attached <u> </u>
No, included in AP ltr <u> </u> |

ACTION PACKAGE CHECKLIST

- Page 2 -

16. INTEGRATED SUMMARY OF EFFECTIVENESS

_____ x _____

17. INTEGRATED SUMMARY OF SAFETY

_____ x _____

revision: 3/7/96

APPEARS THIS WAY
ON ORIGINAL

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

4 pages